

In Vitro Release, pH 3.0, 37°C, paddle

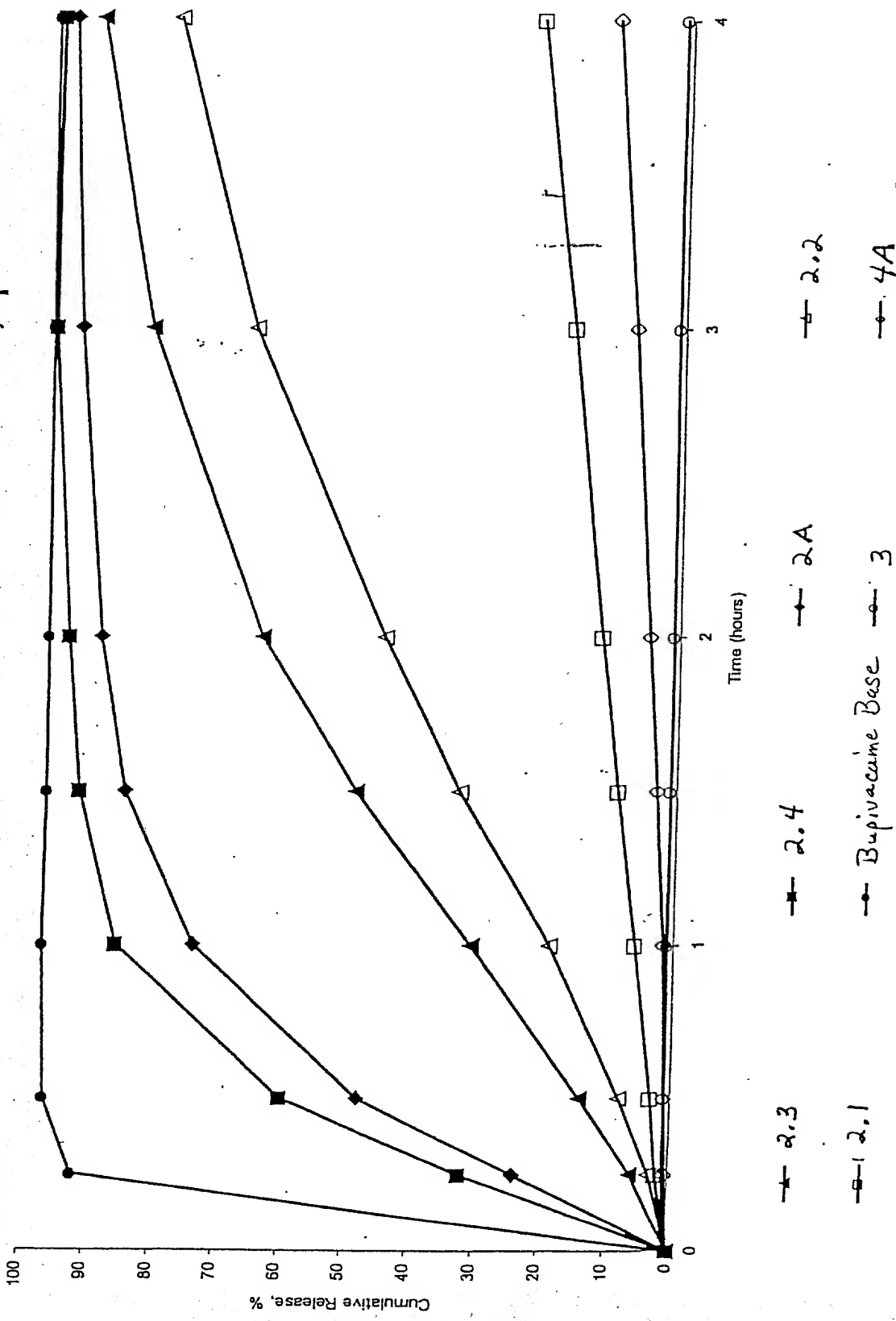


FIG. 1

In Vivo Efficacy, Rat hotplate model Composite

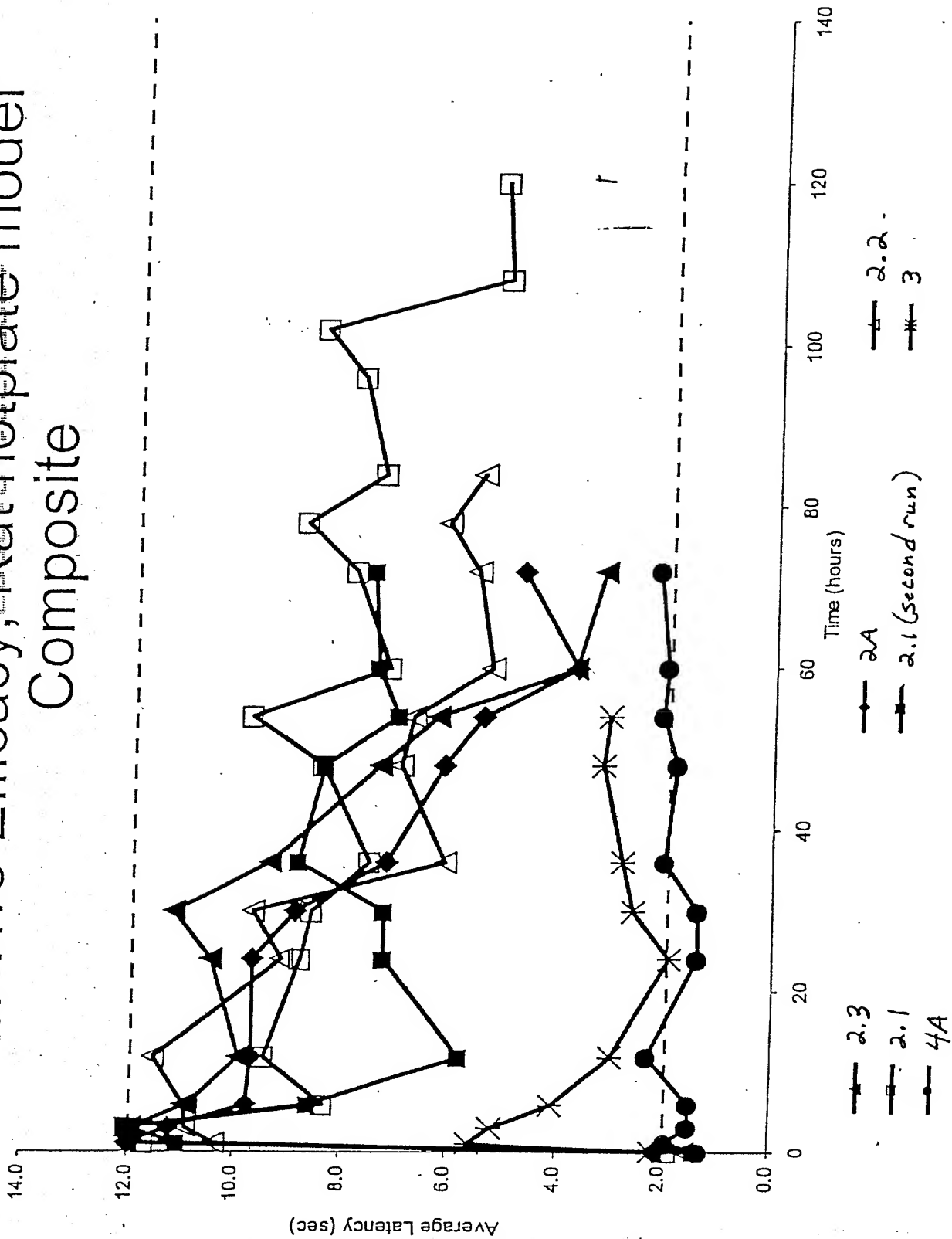


FIG. 2

20031010 10000001

Average release profile of 10 Kg batches in pH 3.0 at 37°C

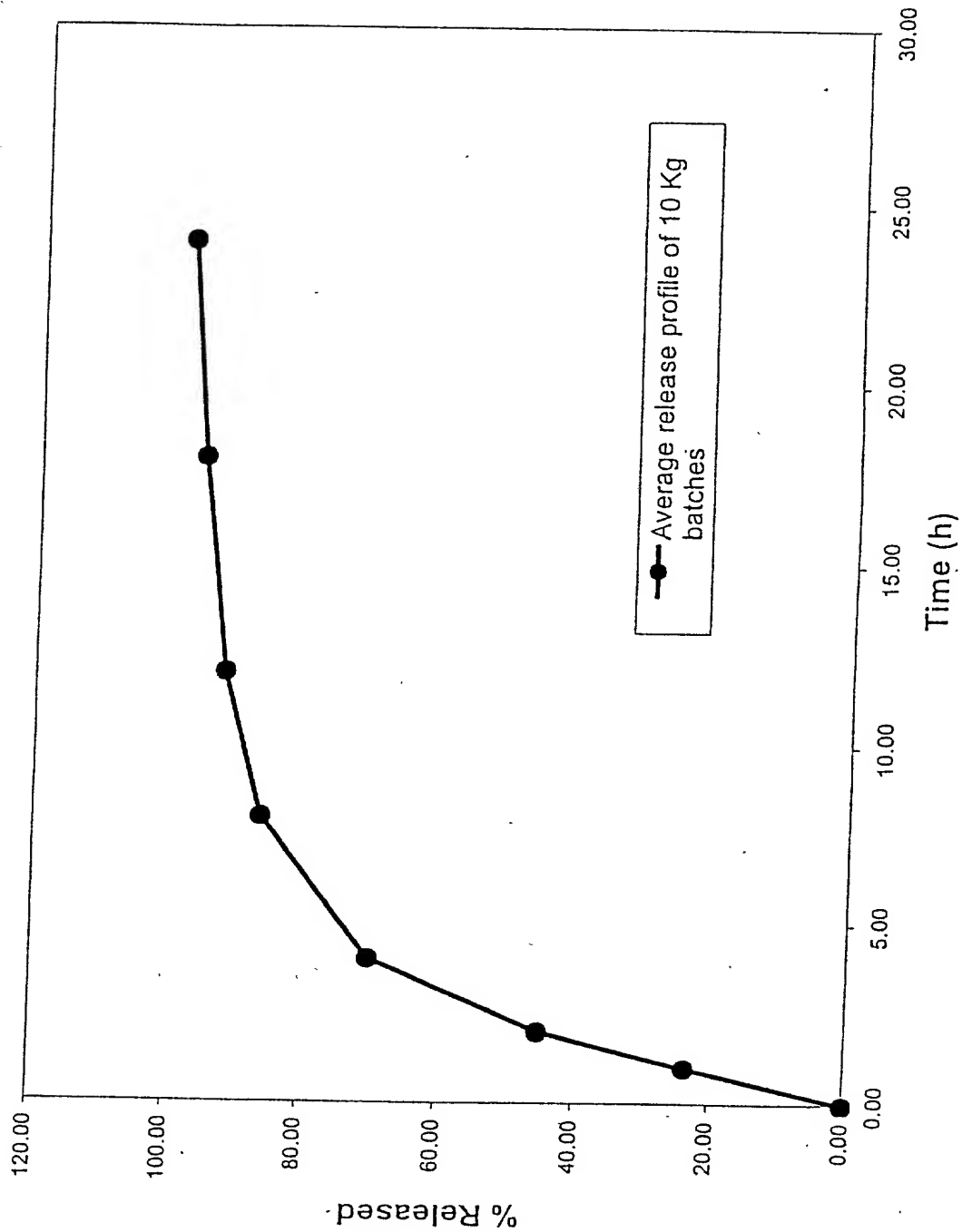


FIG. 3

FIGURE A1

Mean Level Over Time of Median Mechanical Pain Detection Threshold (MPDT)
Part I

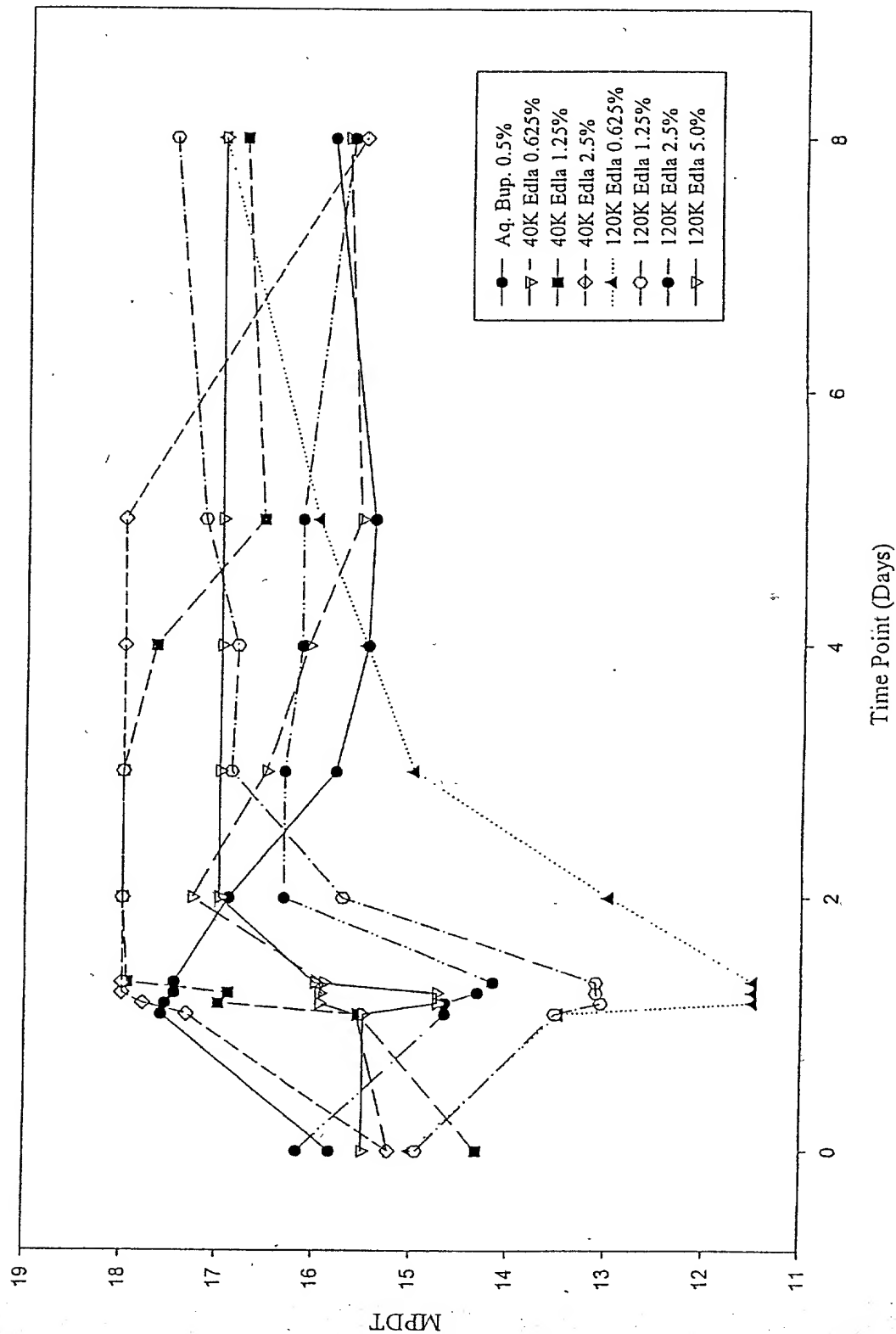


FIGURE A2

Mean Level Over Time of Median Mechanical Pain Detection Threshold (MPDT)
Part II - Bilateral Injection of 40K EDLA and 40K IDLA (one per calf)

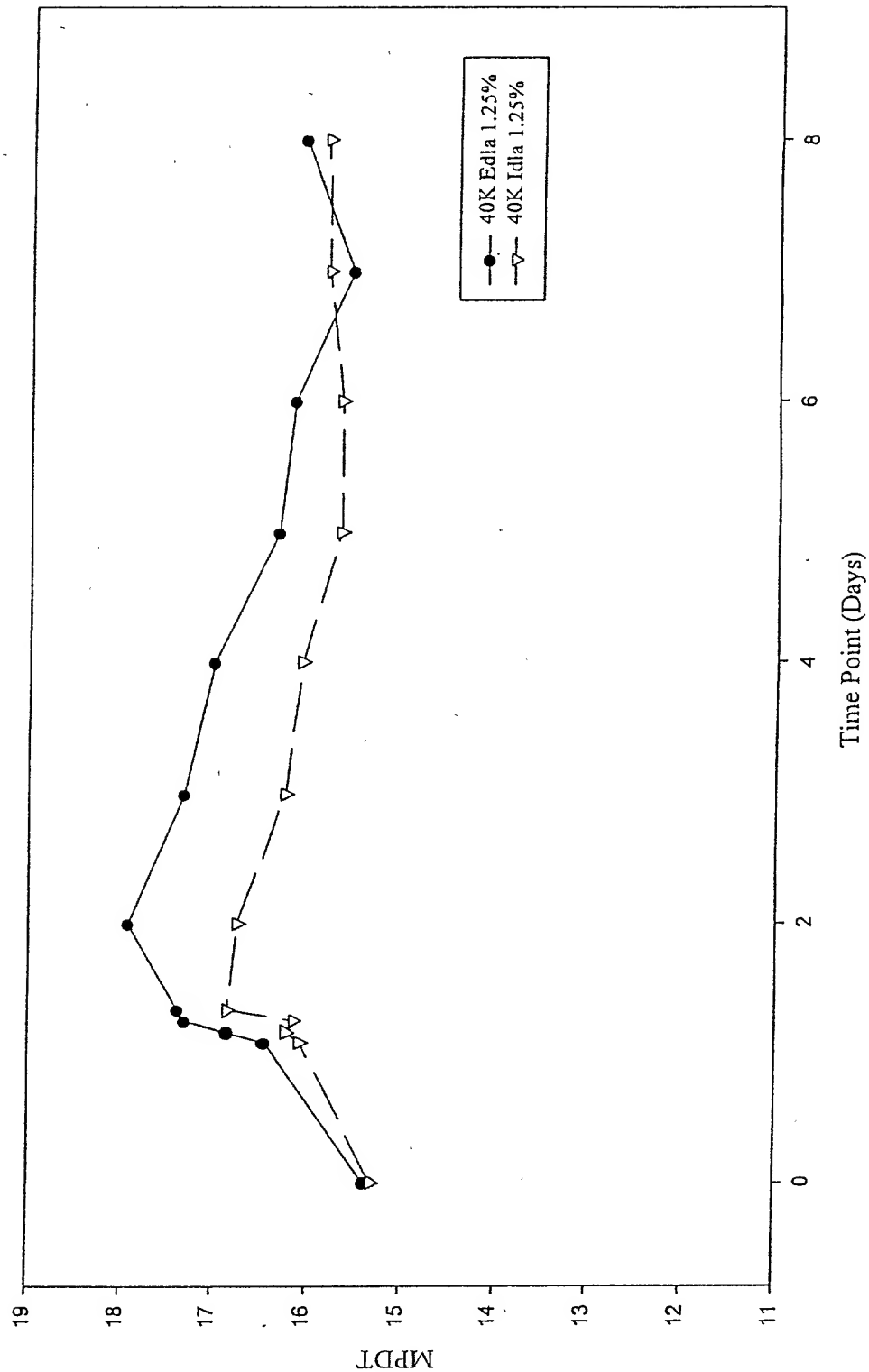
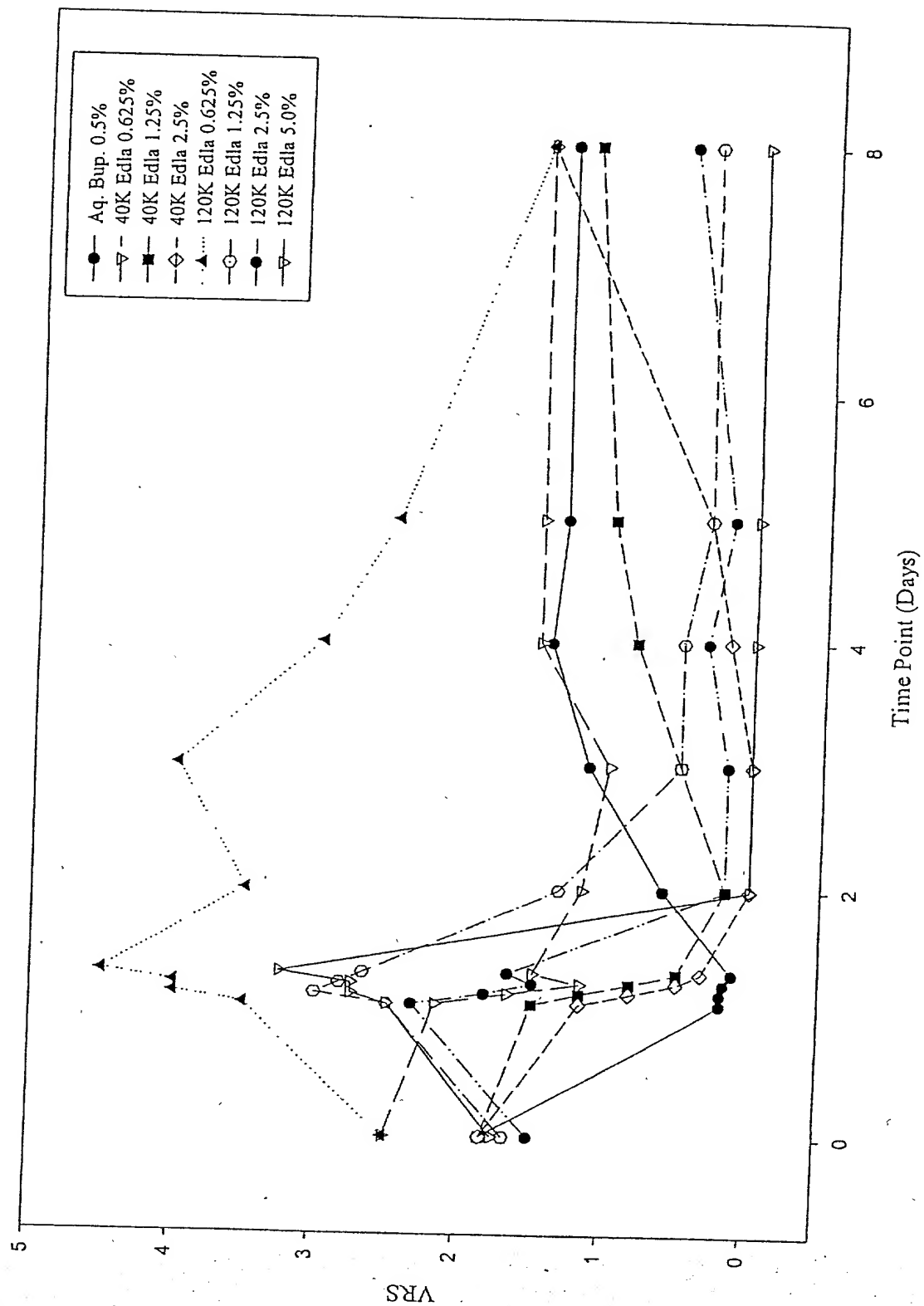
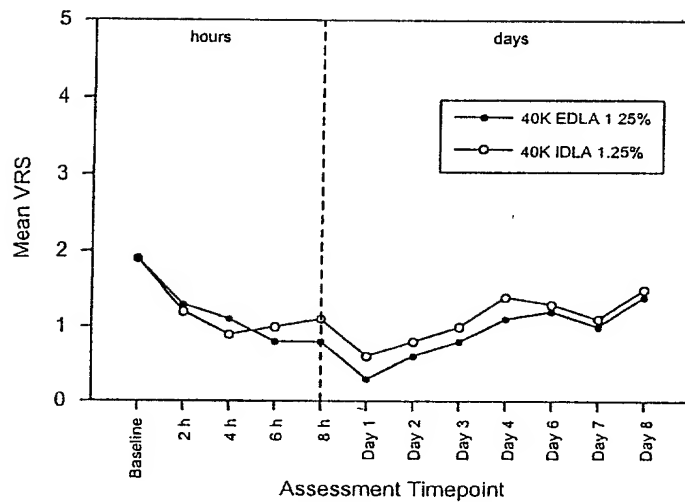


FIGURE A3

Mean Level Over Time of Pain Response to A Single Von Frey Hair
Part I





	Base-line	h 2	h 4	h 6	h 8	h 24	Day 2	Day 3	Day 4	Day 6	Day 7	Day 8
40K EDLA 1.25% N = 13												
VRS												
Mean	1.9	1.3	1.1	0.8	0.8	0.3	0.6	0.8	1.1	1.2	1.0	1.4
(SE)	.3	0.2	0.2	0.2	0.3	0.1	0.4	0.5	0.7	0.6	0.6	0.6
Median	2	1	1	1	1	0	0	0	0	1	0	1
Range	1, 4	0, 2	0, 2	0, 2	0, 3	0, 1	0, 5	0, 6	0, 8	0, 7	0, 7	0, 8
40K IDLA 1.25% N = 13												
VRS												
Mean	1.9	1.2	0.9	1.0	1.1	0.6	0.8	1	1.4	1.3	1.1	1.5
(SE)	0.3	0.2	0.2	0.2	0.3	0.2	0.3	0.3	0.7	0.6	0.7	0.7
Median	2	1	1	1	1	1	1	1	1	1	0	1
Range	1, 4	0, 3	0, 2	0, 2	0, 3	0, 2	0, 3	0, 4	0, 9	0, 8	0, 8	0, 9

FIGURE A4

FIGURE A5

Mean Level Over Time of Median Mechanical Touch Detection Threshold (MTDT)
Part I

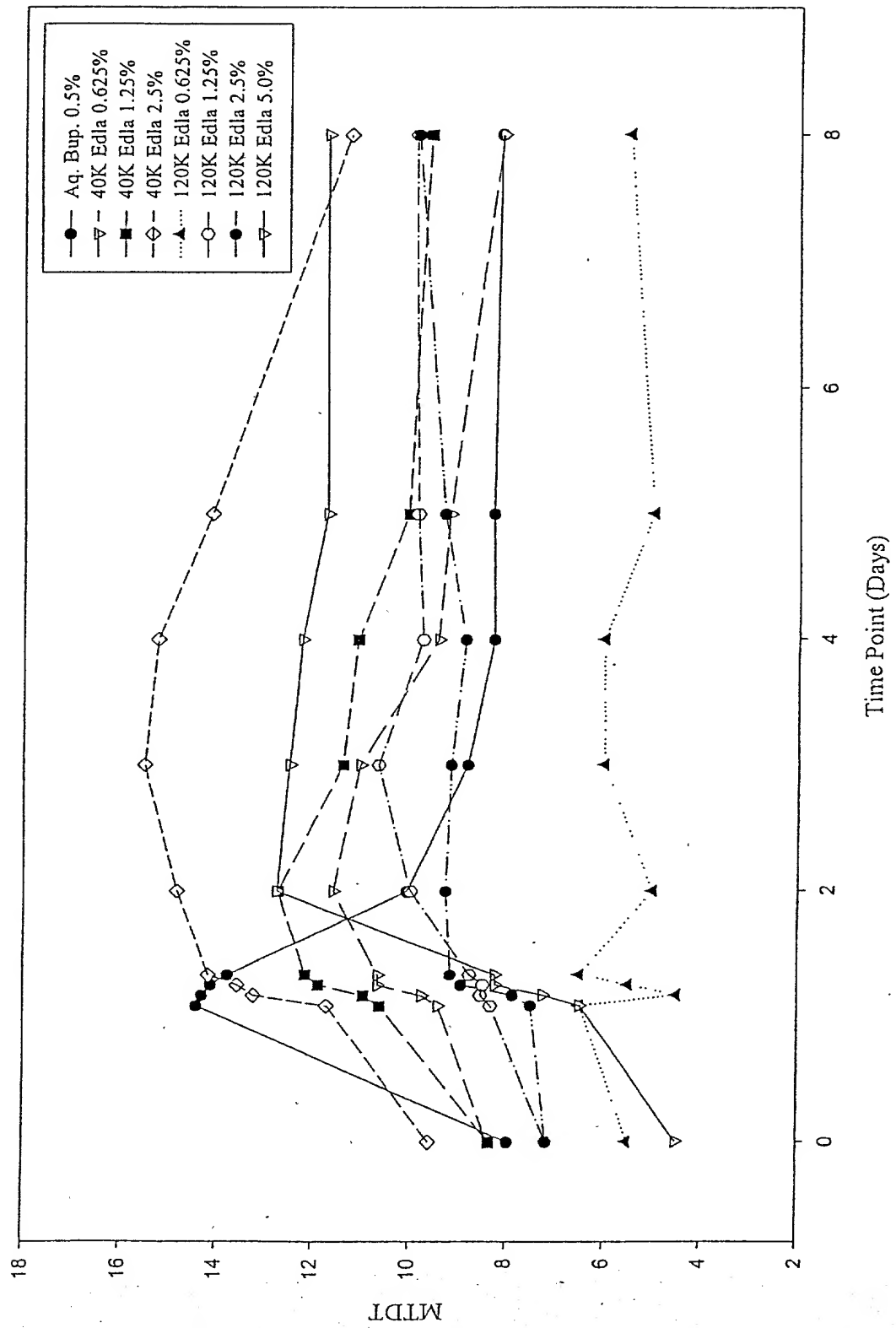
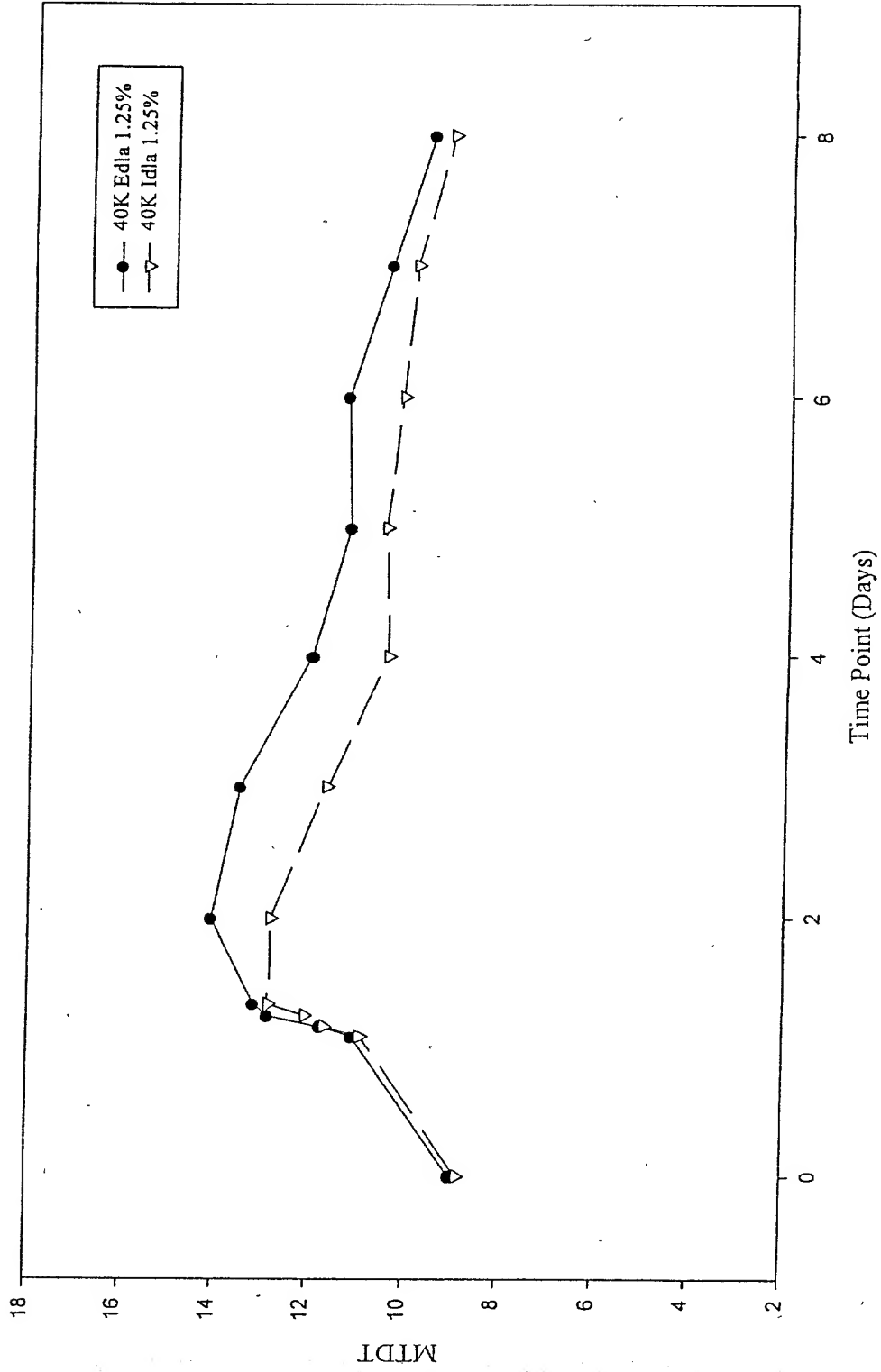


FIGURE A6

Mean Level Over Time of Median Mechanical Touch Detection Threshold (MTDT)
Part II - Bilateral Injection of 40K EDLA and 40K IDLA (one per calf)



Mean Level Over Time of Suprathreshold Pain Response to Heat for Study Part I

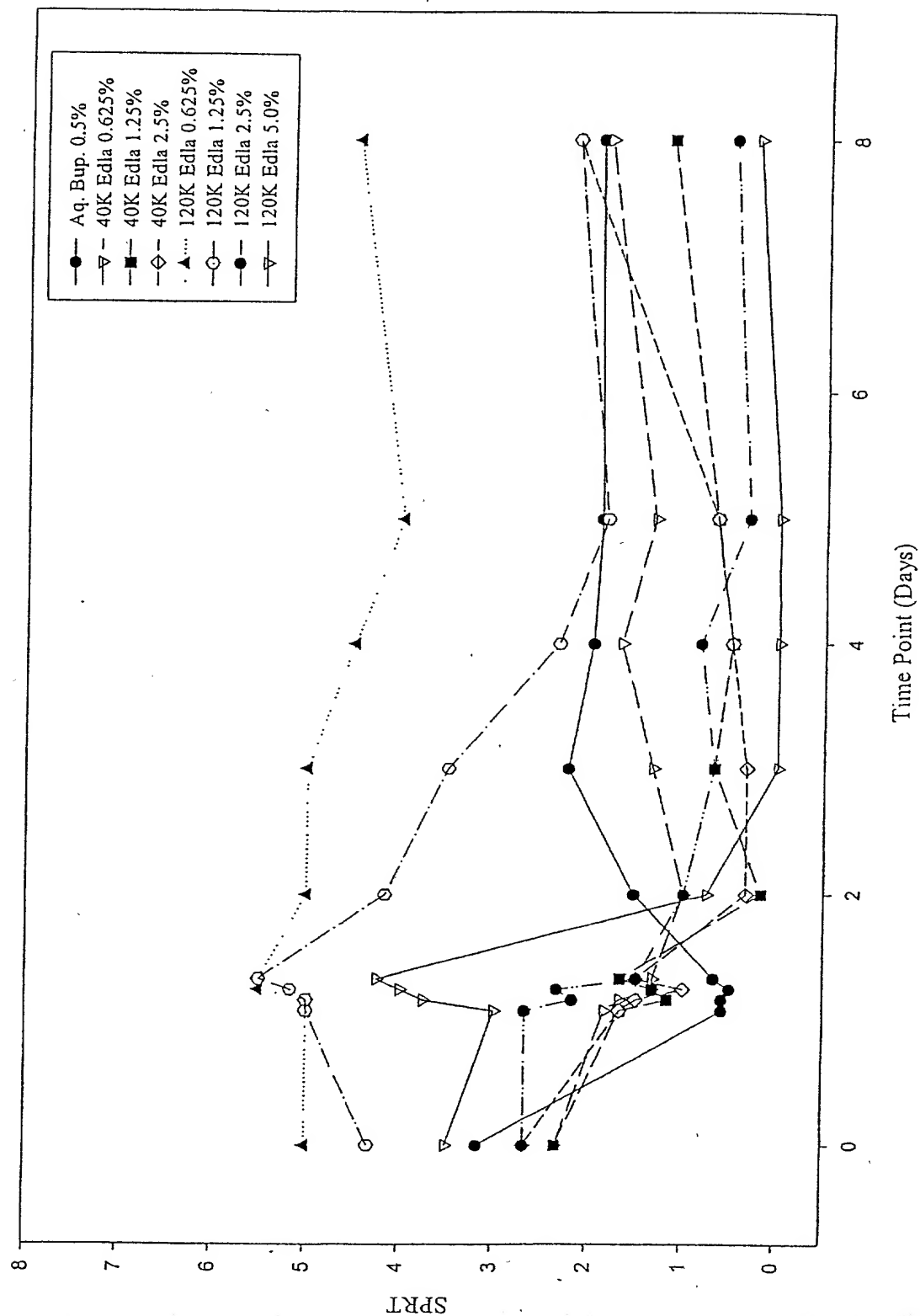
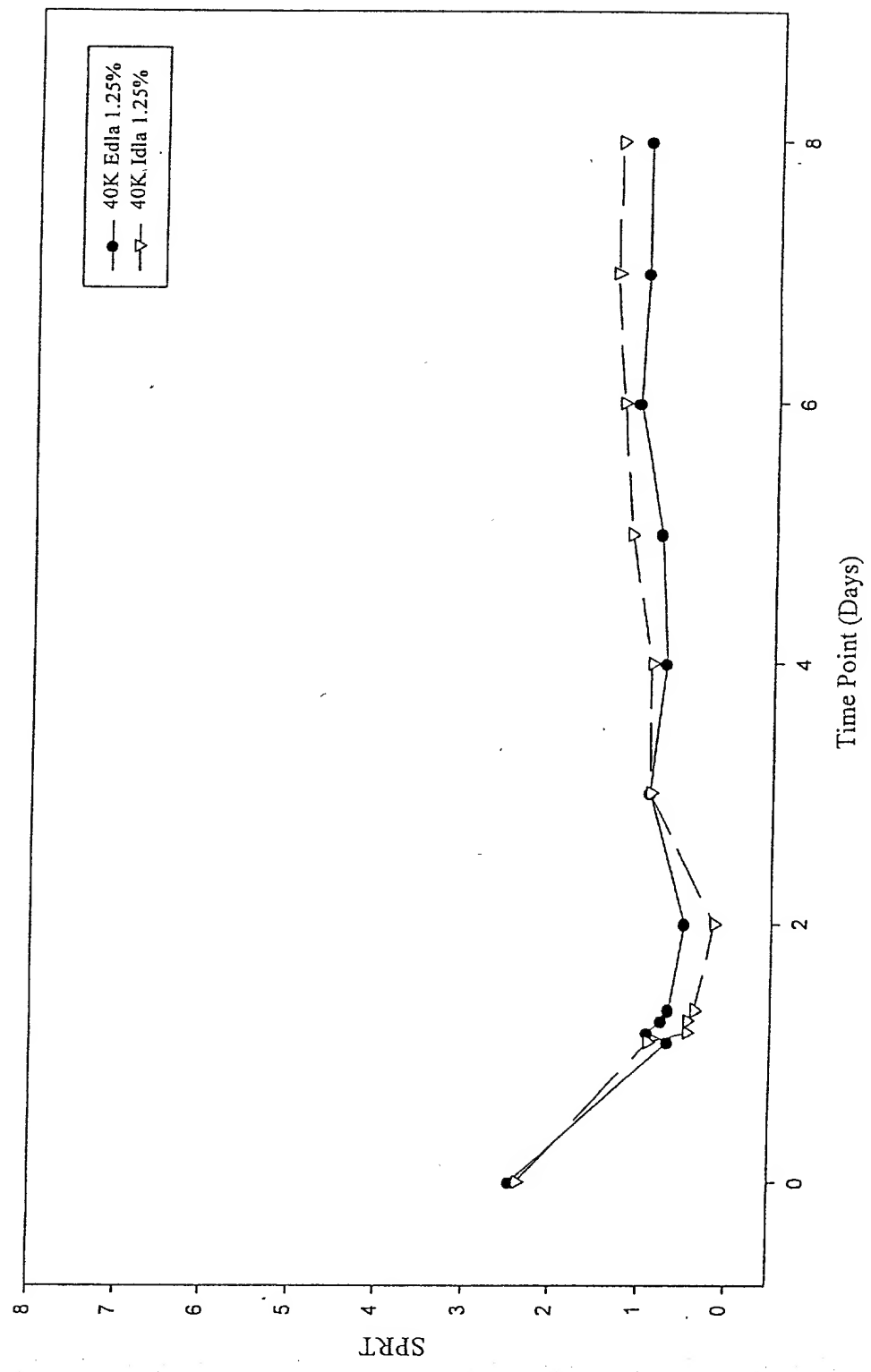
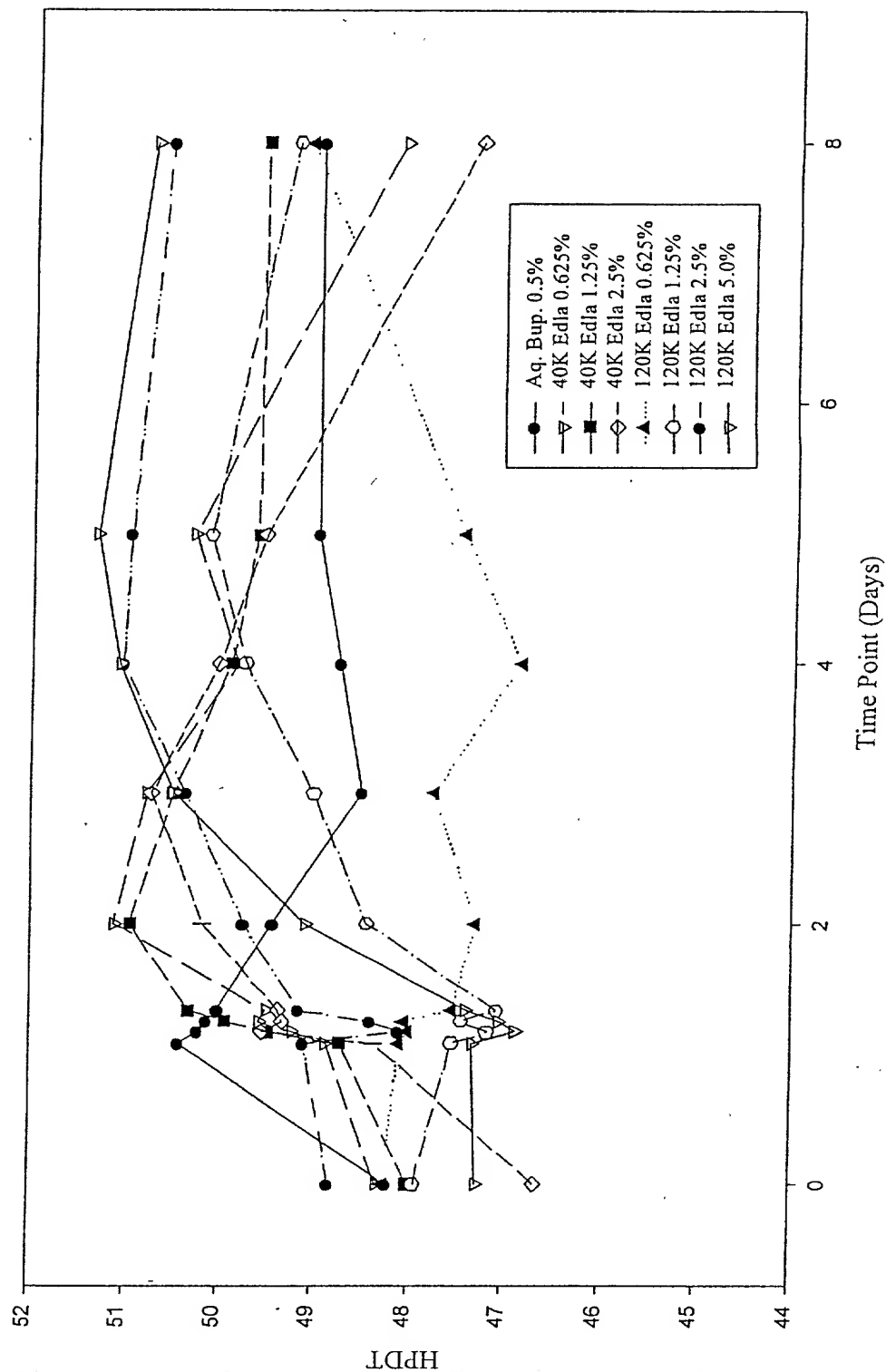


FIGURE A8

Mean Level Over Time of Suprathreshold Pain Response to Heat for Study
Part II - Bilateral Injection of 40K EDLA and 40K IDLA (one per calf)



Mean Level Over Time of Heat Pain Detection Threshold (HPDT) Part I



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FIGURE A10

Mean Level Over Time of Heat Pain Detection Threshold (HPDT)
Part II - Bilateral Injection of 40K EDLA and 40K IDLA (one per calf)

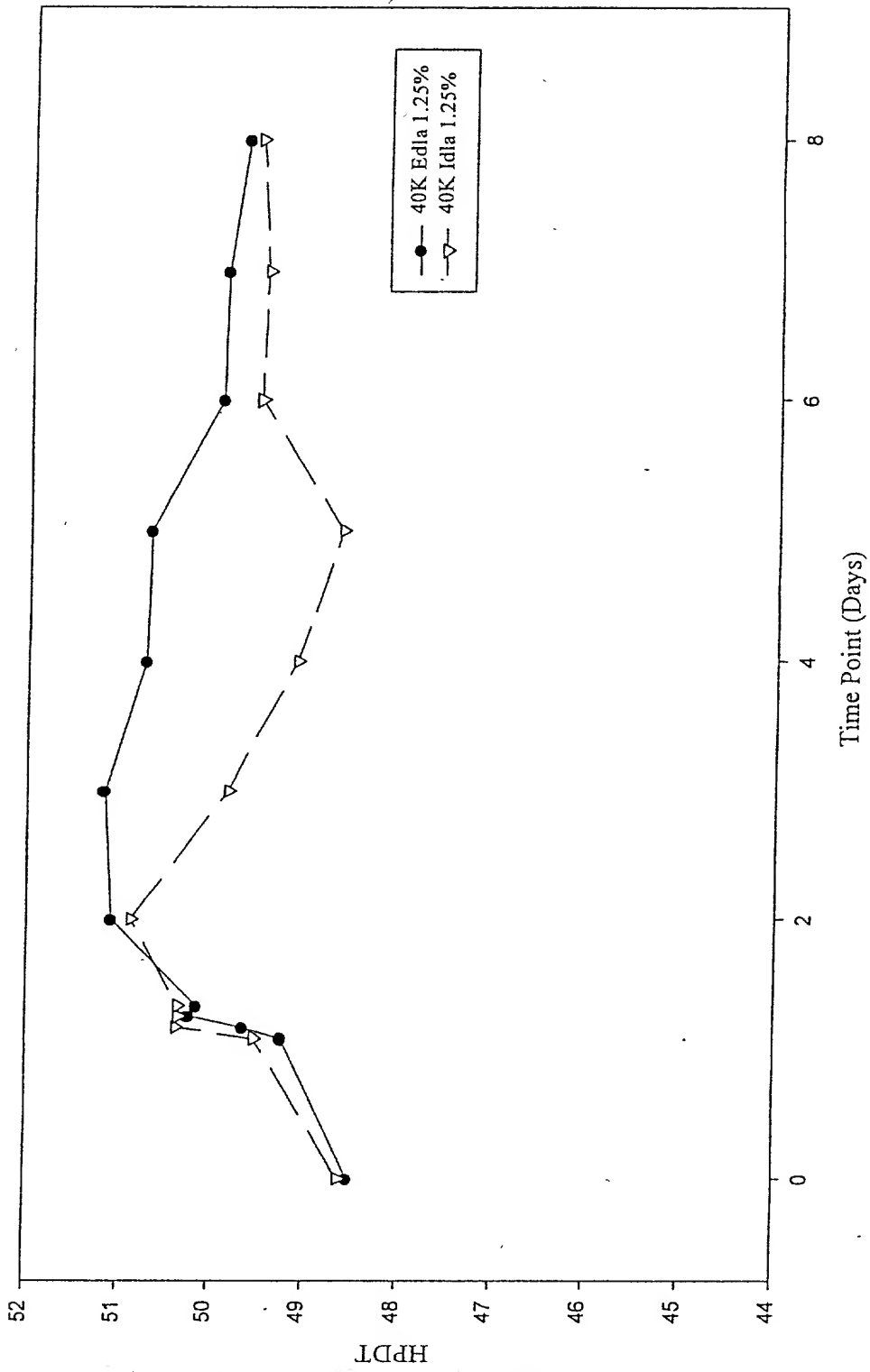


FIGURE A11

Mean Level Over Time of Median Warm Detection Threshold (WDT)
Part I

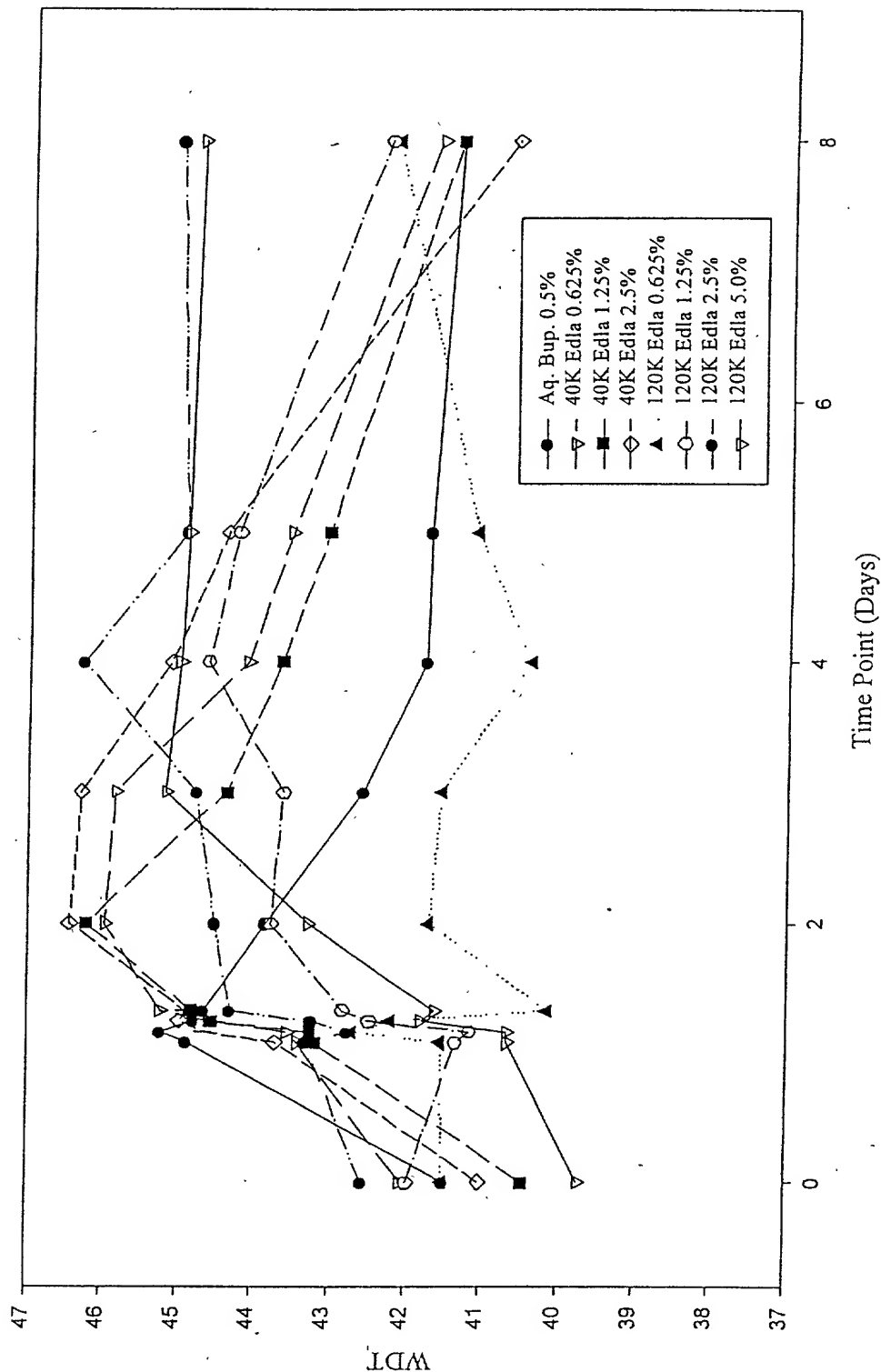


FIGURE A12

Mean Level Over Time of Median Warm Detection Threshold (WDT)
Part II - Bilateral Injection of 40K EDLA and 40K IDLA (one per calf)

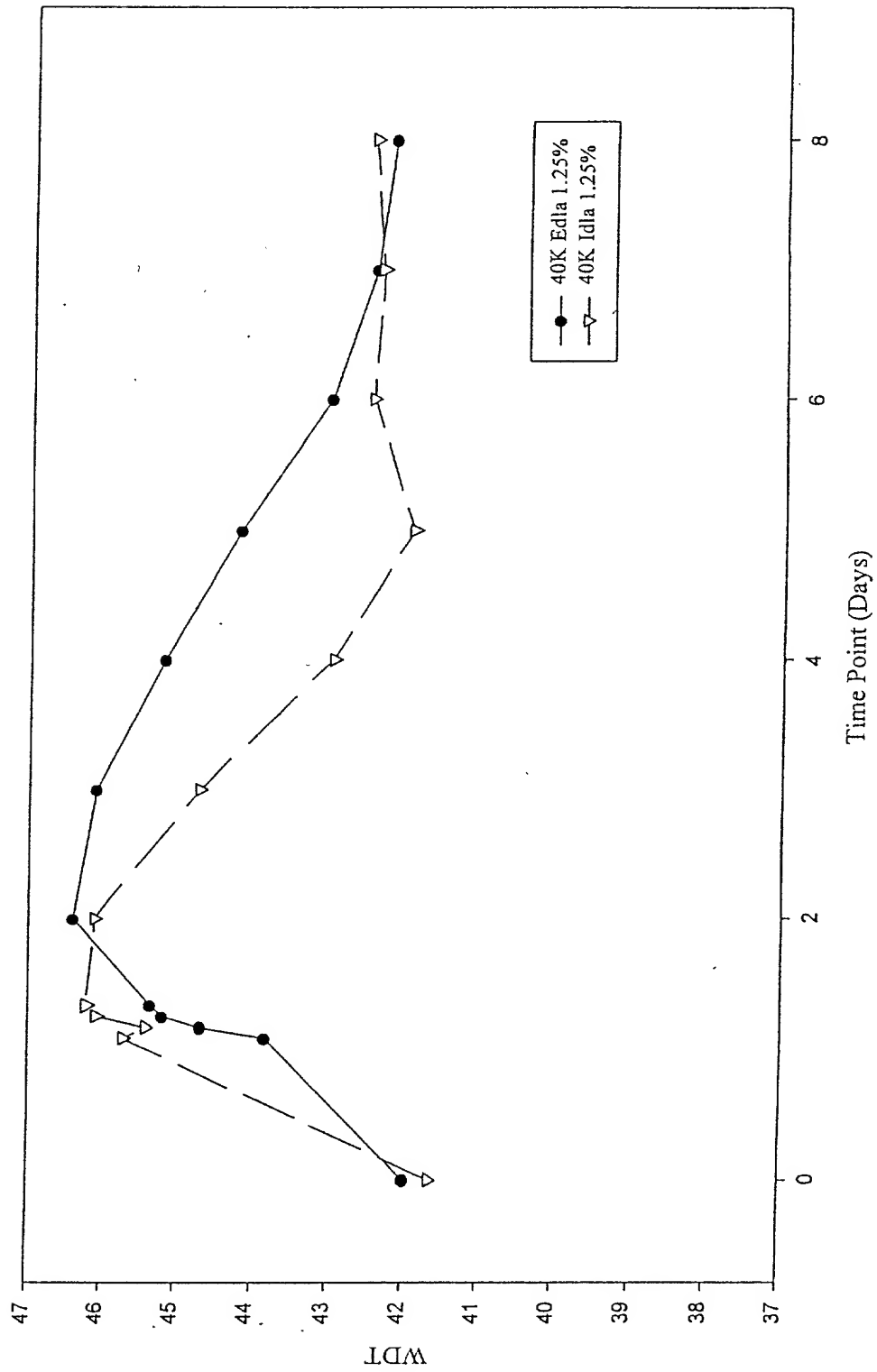
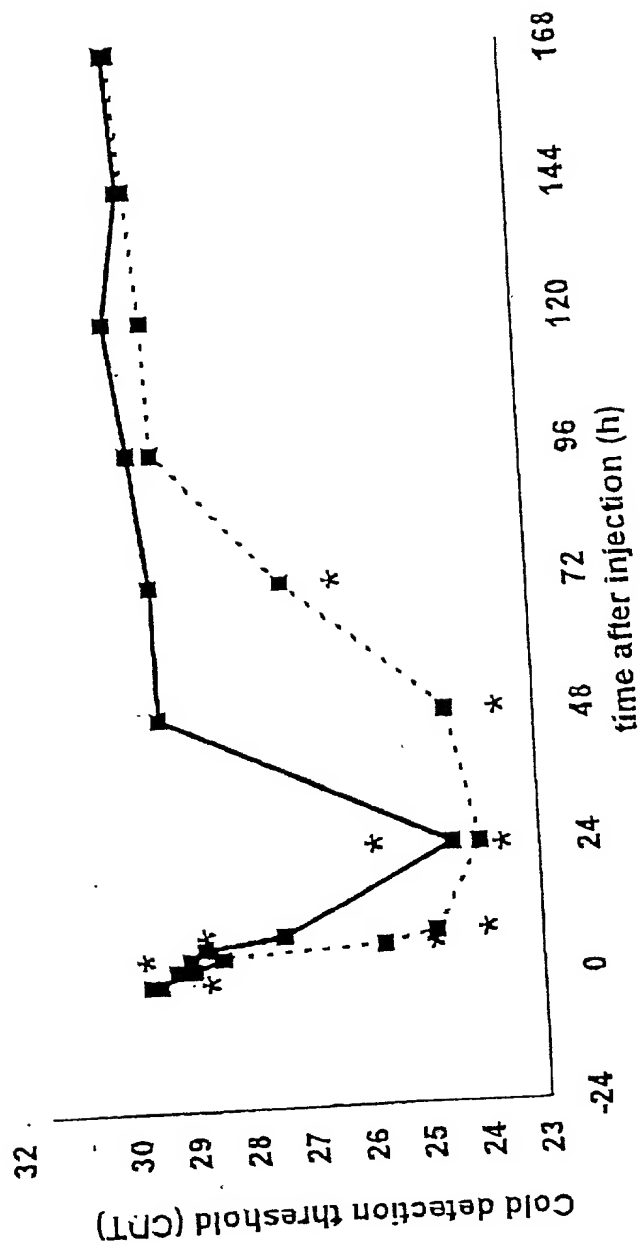
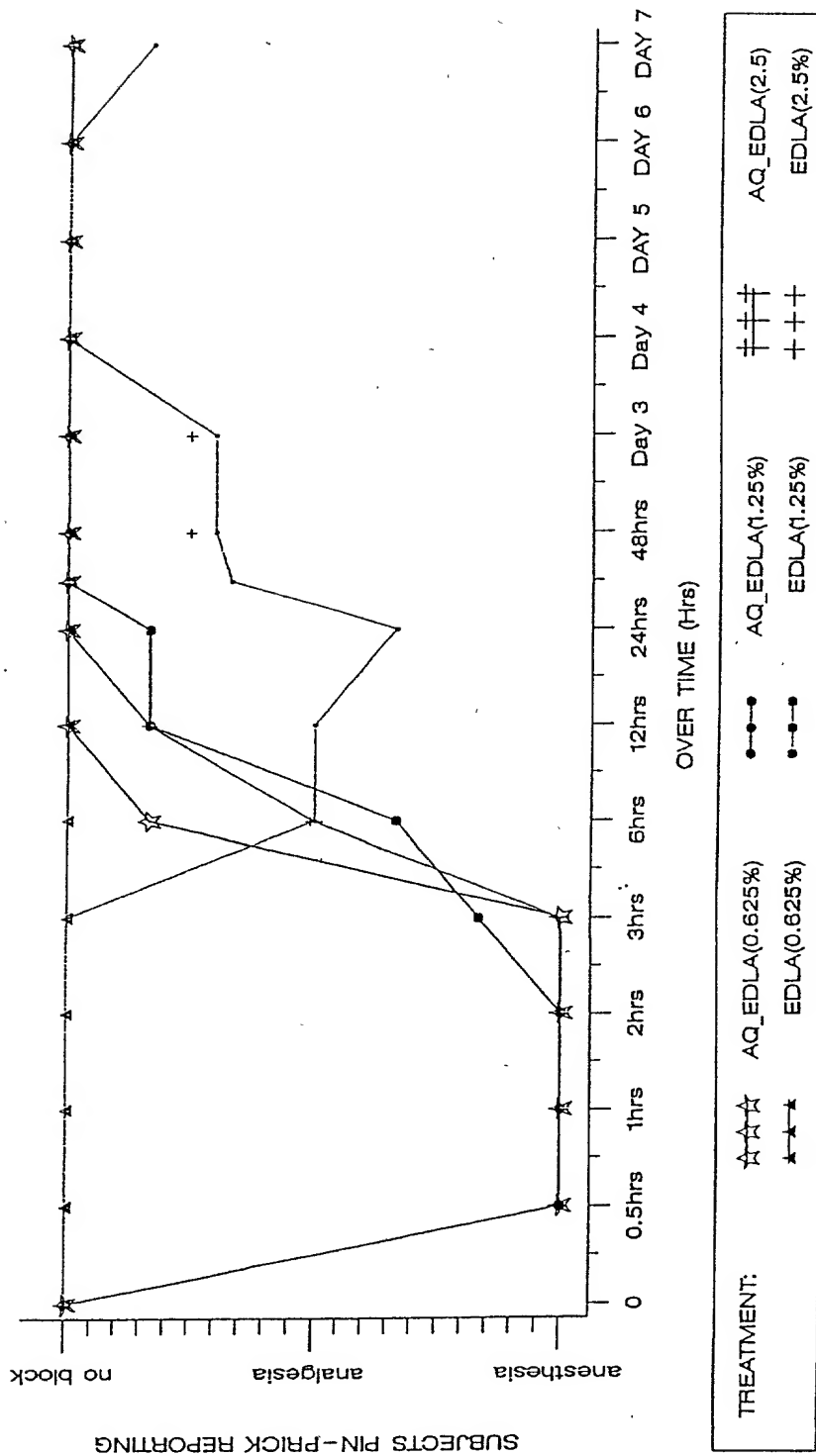


FIGURE A13



MEAN LEVEL OF ANALGESIA/ANESTHESIA(PIN -PRICK TEST) OVER TIME BY TREATMENT

Population: All Subjects Enrolled In Study
STUDY PHASE=1 FORMULA=120K



MEAN LEVEL OF ANALGESIA/ANESTHESIA(PIN - PRICK TEST) OVER TIME BY TREATMENT

Population: All Subjects Enrolled In Study

STUDY PHASE=1 FORMULA=40K

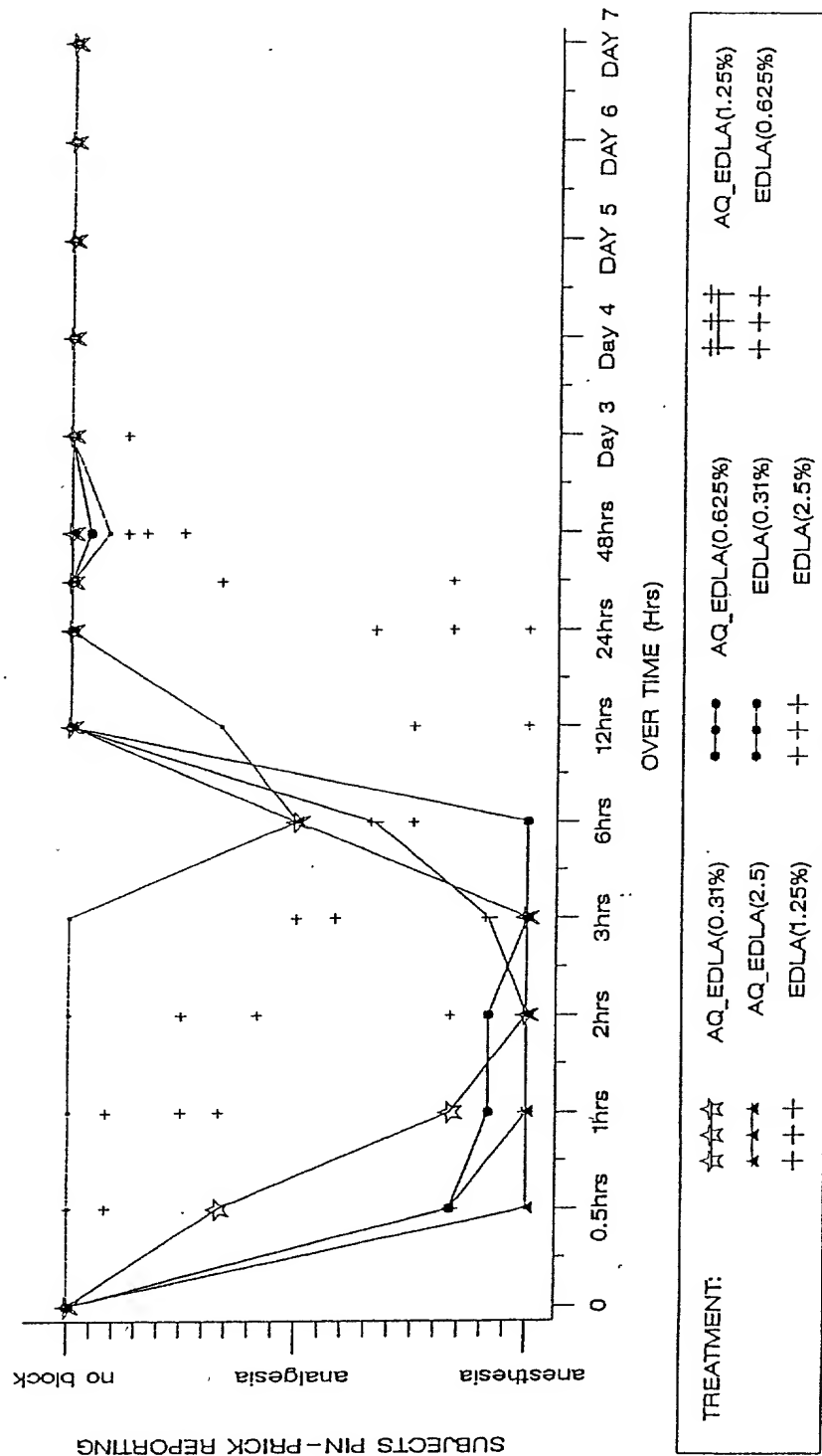
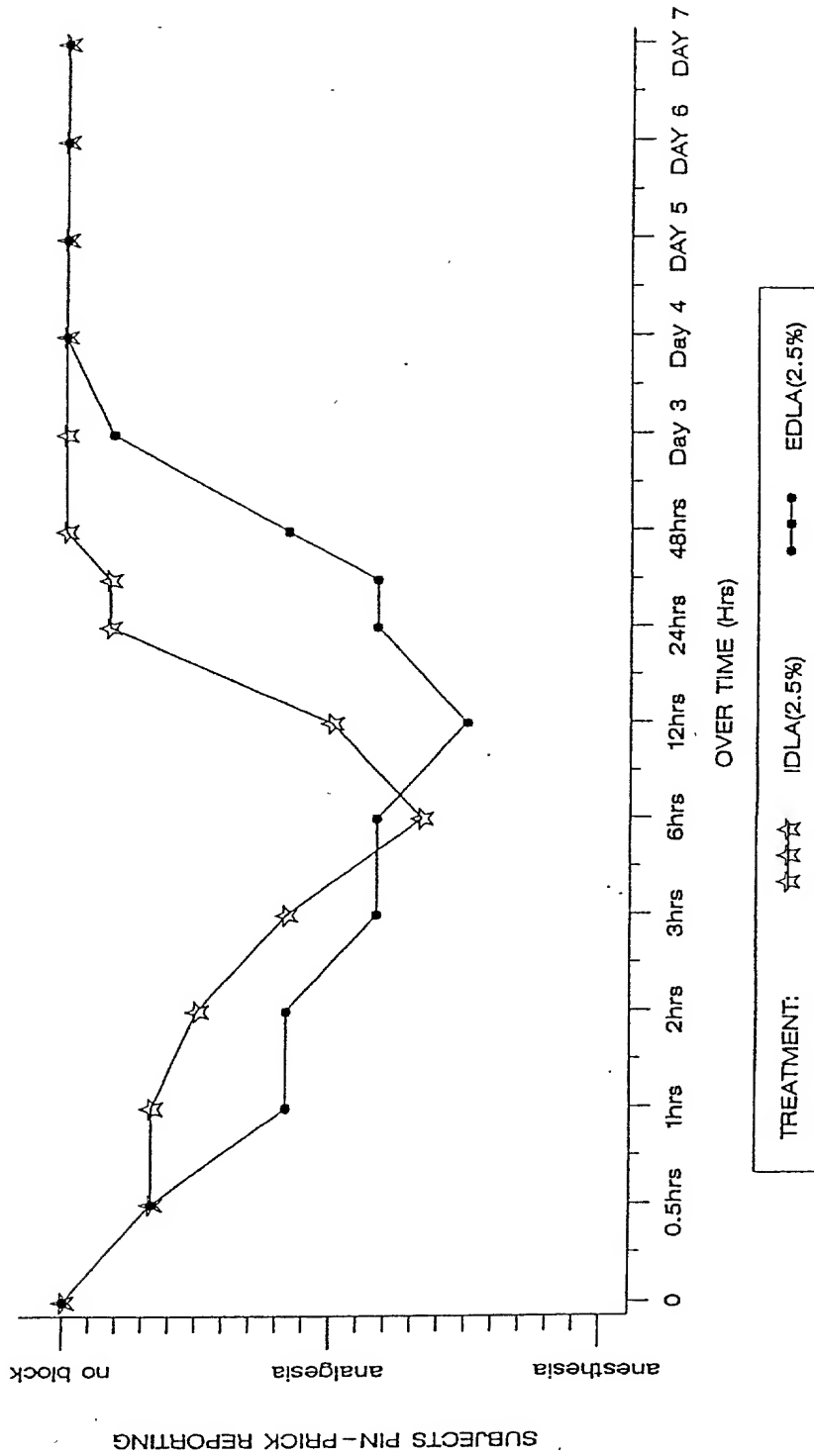


FIGURE C3

MEAN LEVEL OF ANALGESIA/ANESTHESIA(PIN-PRICK TEST) OVER TIME BY TREATMENT

Population: All Subjects Enrolled In Study
STUDY PHASE=2 FORMULA=40K



2005-07-10 10:45:00

FIGURE C4

MEAN LEVEL OF ANALGESIA/ANESTHESIA(PIN - PRICK TEST) OVER TIME BY TREATMENT

Population: All Subjects Enrolled in Study
STUDY PHASE = 2 FORMULA = 120K

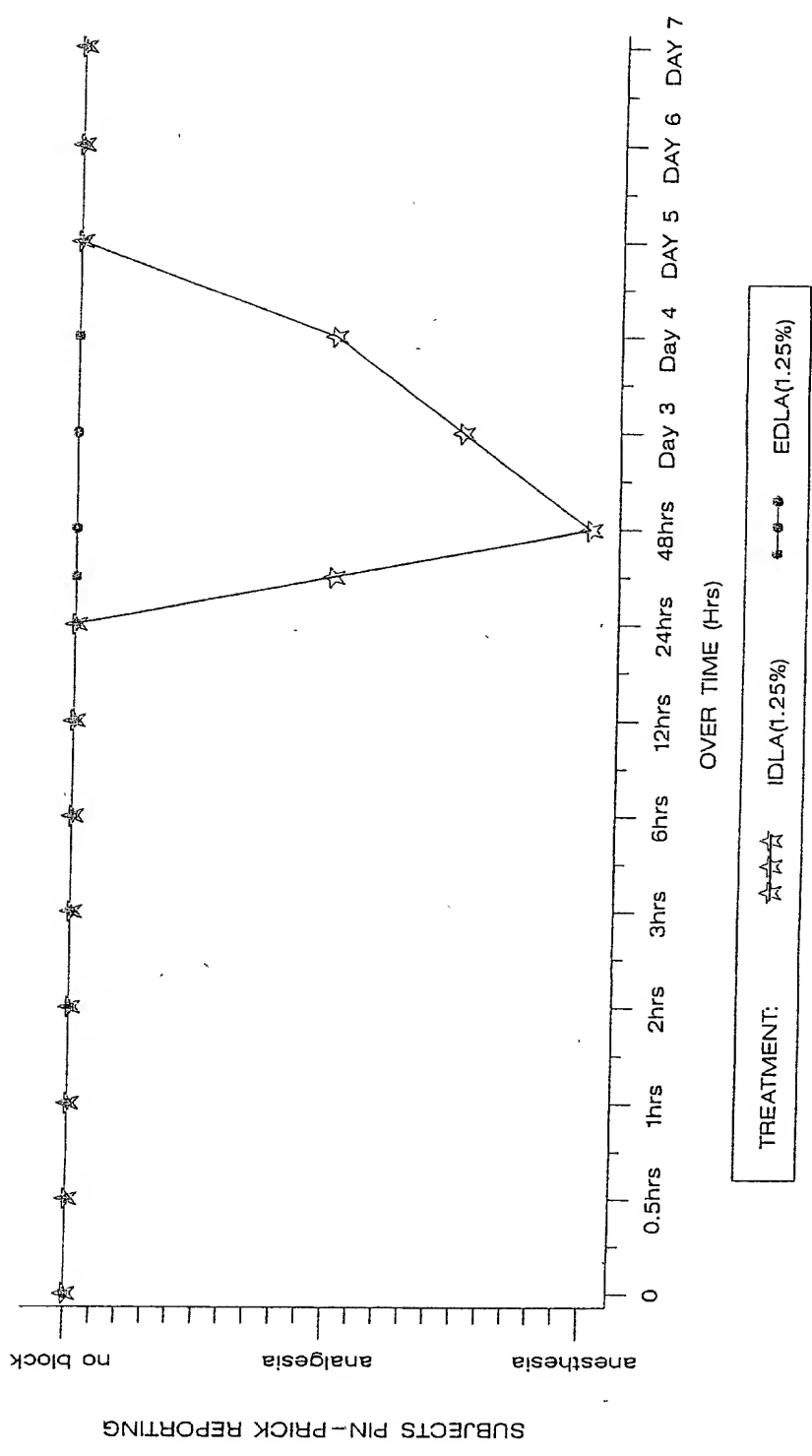
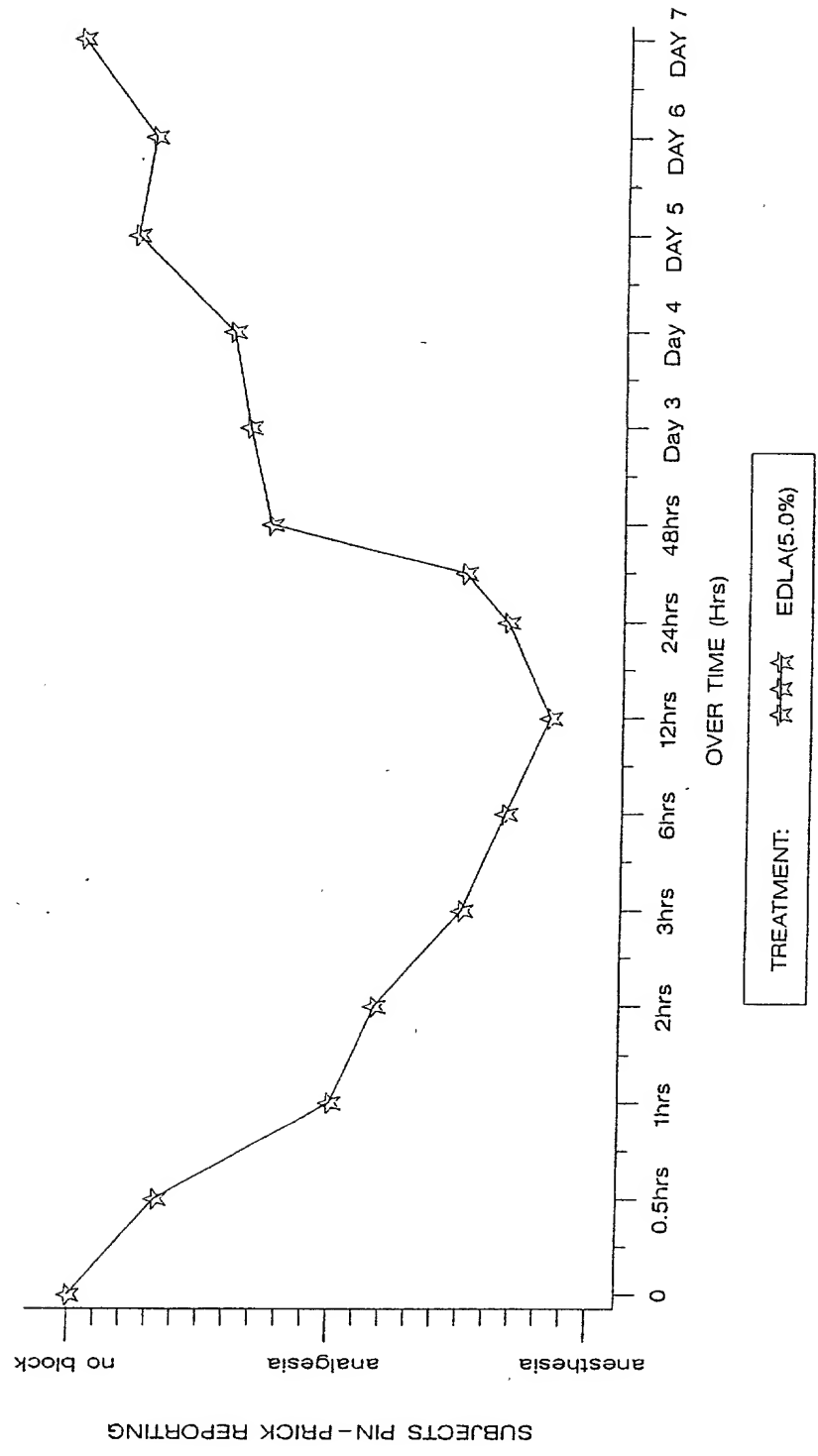
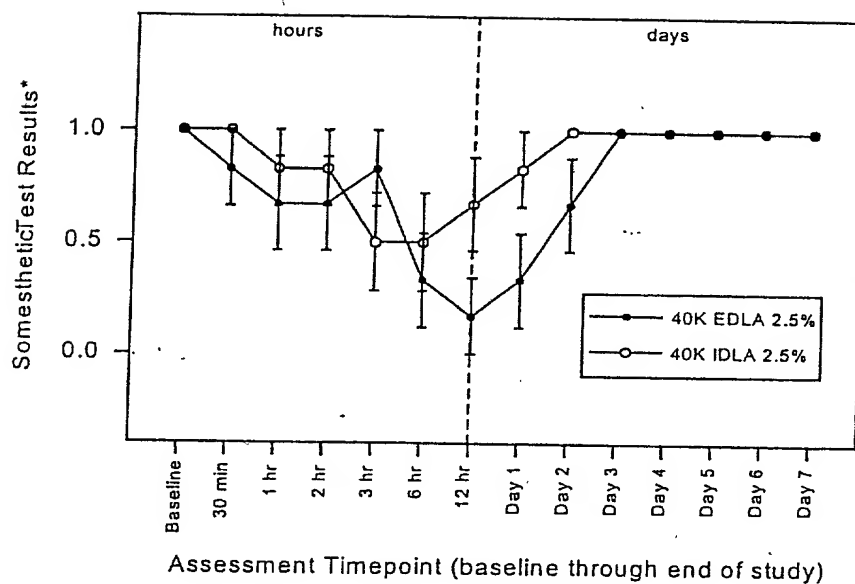


FIGURE C5

MEAN LEVEL OF ANALGESIA/ANESTHESIA(PIN - PRICK TEST) OVER TIME BY TREATMENT

Population: All Subjects Enrolled in Study
STUDY PHASE = 3 FORMULA = 40K





	Base-line	30 min	Hr 1	Hr 2	Hr 3	Hr 6	Hr 12	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
40K EDLA 2.5%														
N=6														
Somesthetic Test Results ^a														
Mean	1.0	0.8	0.7	0.7	0.8	0.3	0.2	0.3	0.7	1.0	1.0	1.0	1.0	1.0
(SE)	(0)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0)	(0)	(0)	(0)	(0)
Minimum	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	1.0	1.0	1.0	1.0
Maximum	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
40K IDLA 2.5%														
N=6														
Somesthetic Test Results ^a														
Mean	1.0	1.0	0.8	0.8	0.5	0.5	0.7	0.8	1.0	1.0	1.0	1.0	1.0	1.0
(SE)	(0)	(0)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0)	(0)	(0)	(0)	(0)	(0)
Minimum	1.0	1.0	0.0	0.0	0.0	0.0	0.0	0.0	1.0	1.0	1.0	1.0	1.0	1.0
Maximum	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

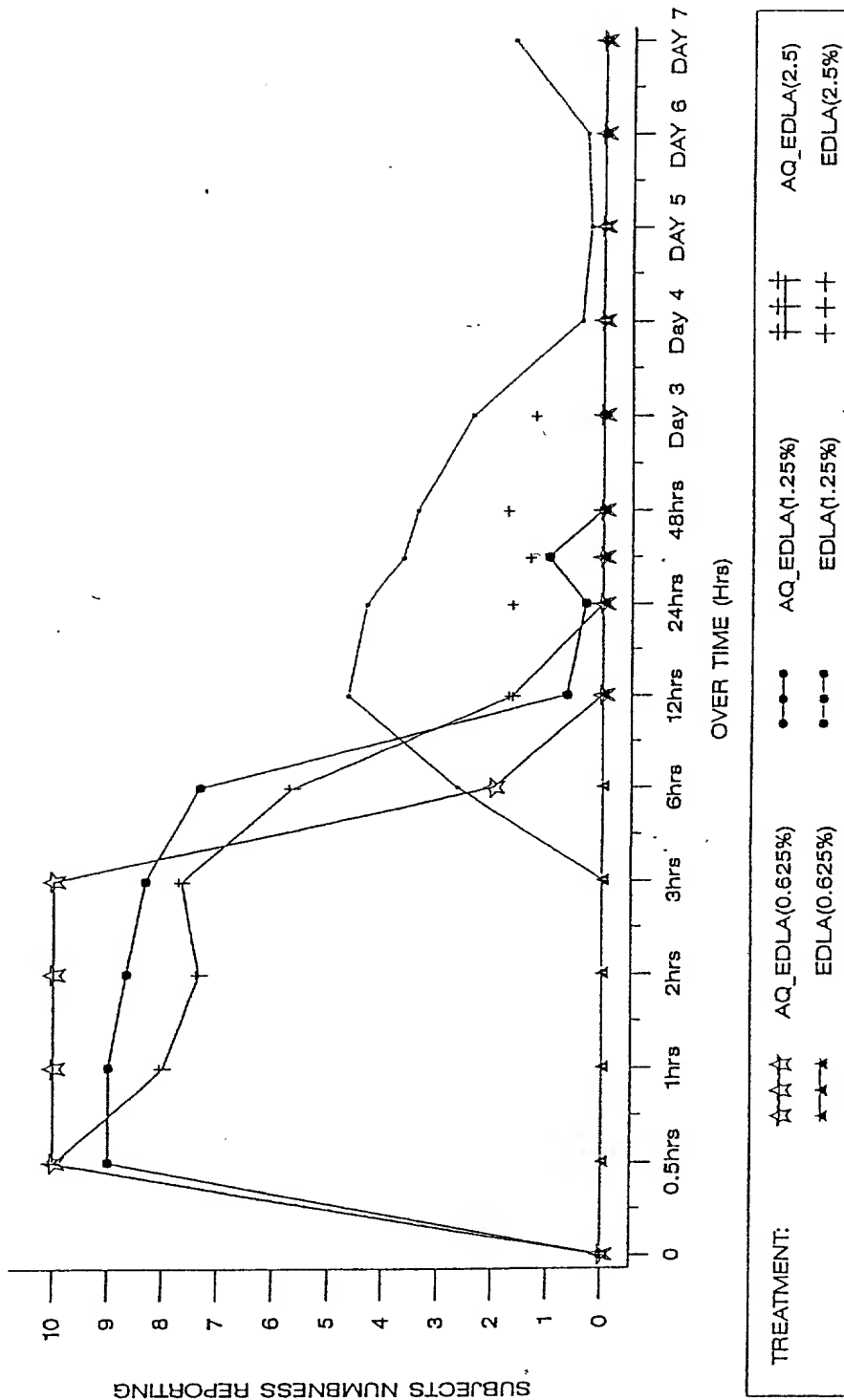
^a Evaluated on a scale of 0-2, with 0 = no feeling; 1 = feels touch/pressure; 2 = feels sharp.

FIGURE C6

FIGURE C7

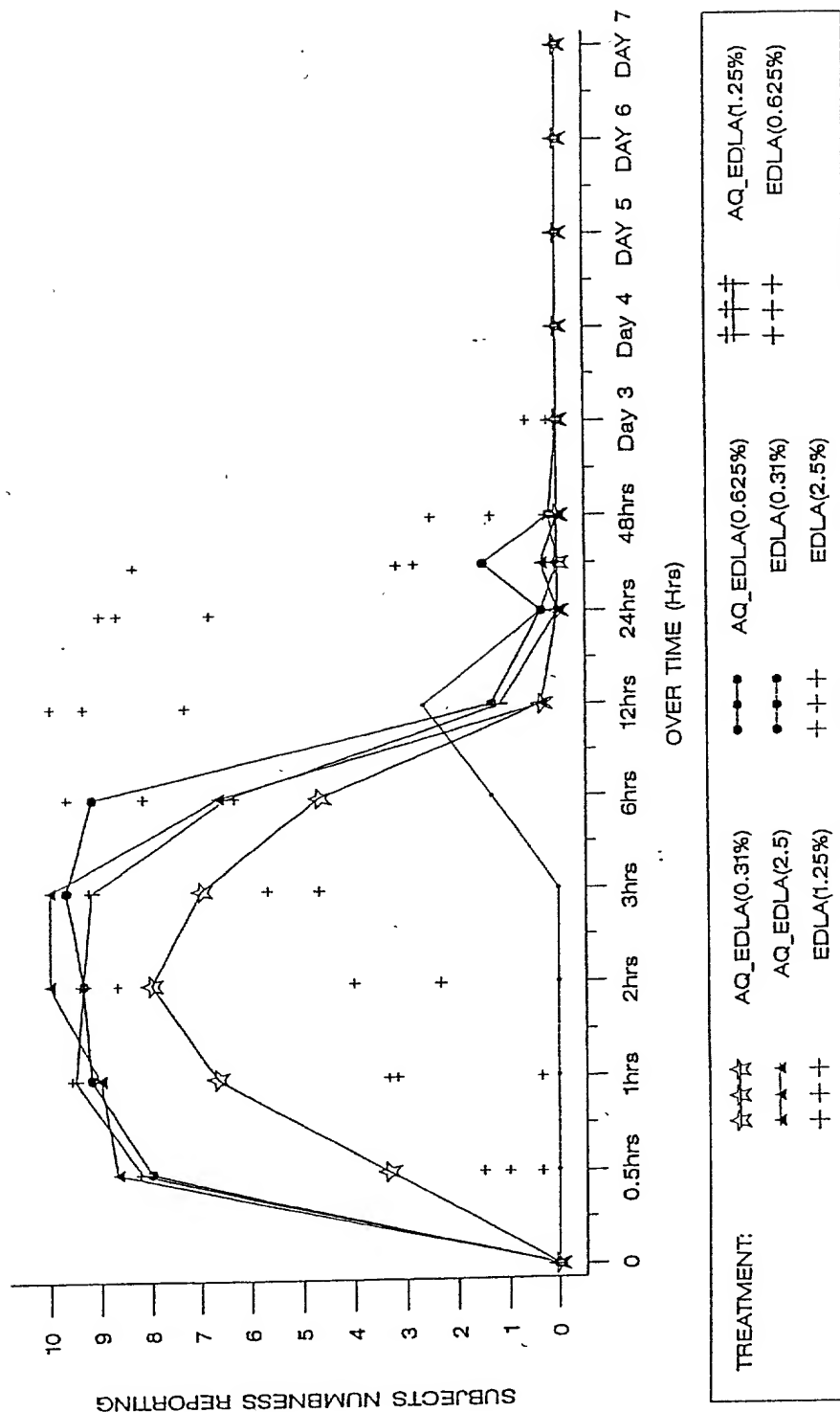
MEAN LEVEL OF NUMBNESS OVER TIME BY TREATMENT

Population: All Subjects Enrolled In Study
STUDY PHASE-1 FORMULA-120K



MEAN LEVEL OF NUMBNESS OVER TIME BY TREATMENT

Population: All Subjects Enrolled In Study
STUDY PHASE=1 FORMULA=40K



MEAN PLASMA CONCENTRATIONS OF BUPIVACAINE (ng/ml) BY TIME POINT

Population: All Subjects Enrolled in Study
STUDY PHASE=2 FORMULA=40K

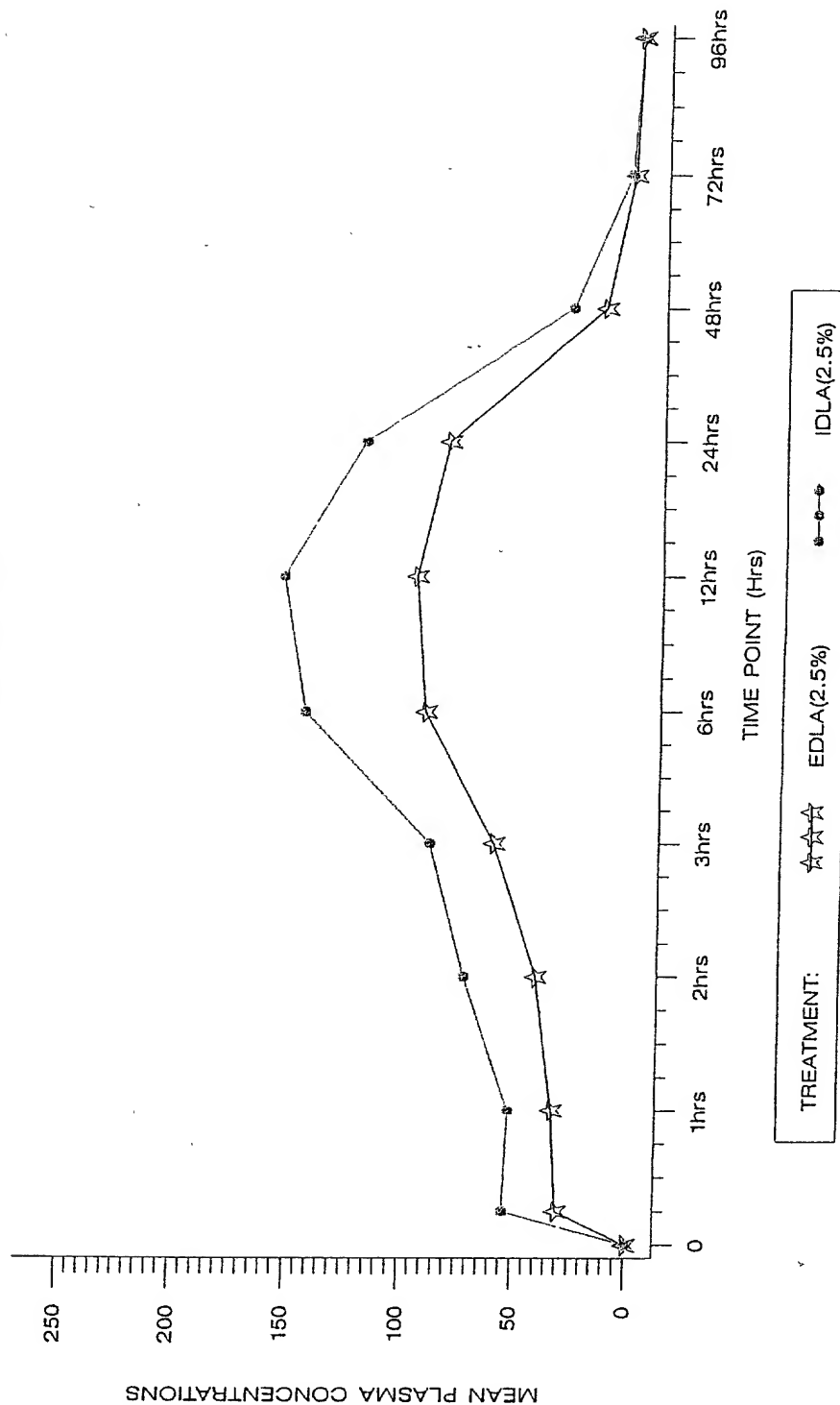
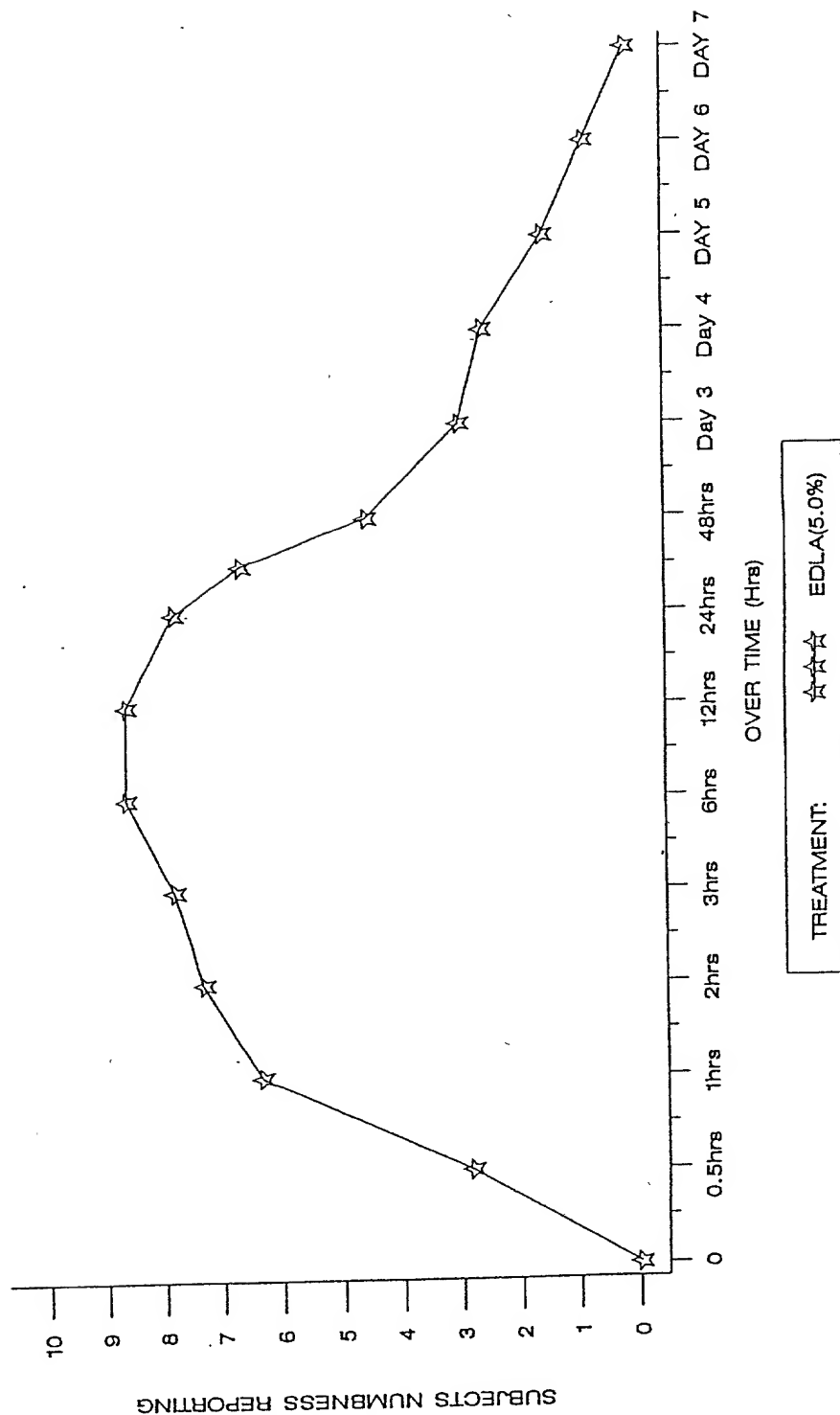


FIGURE C10

MEAN LEVEL OF NUMBNESS OVER TIME BY TREATMENT

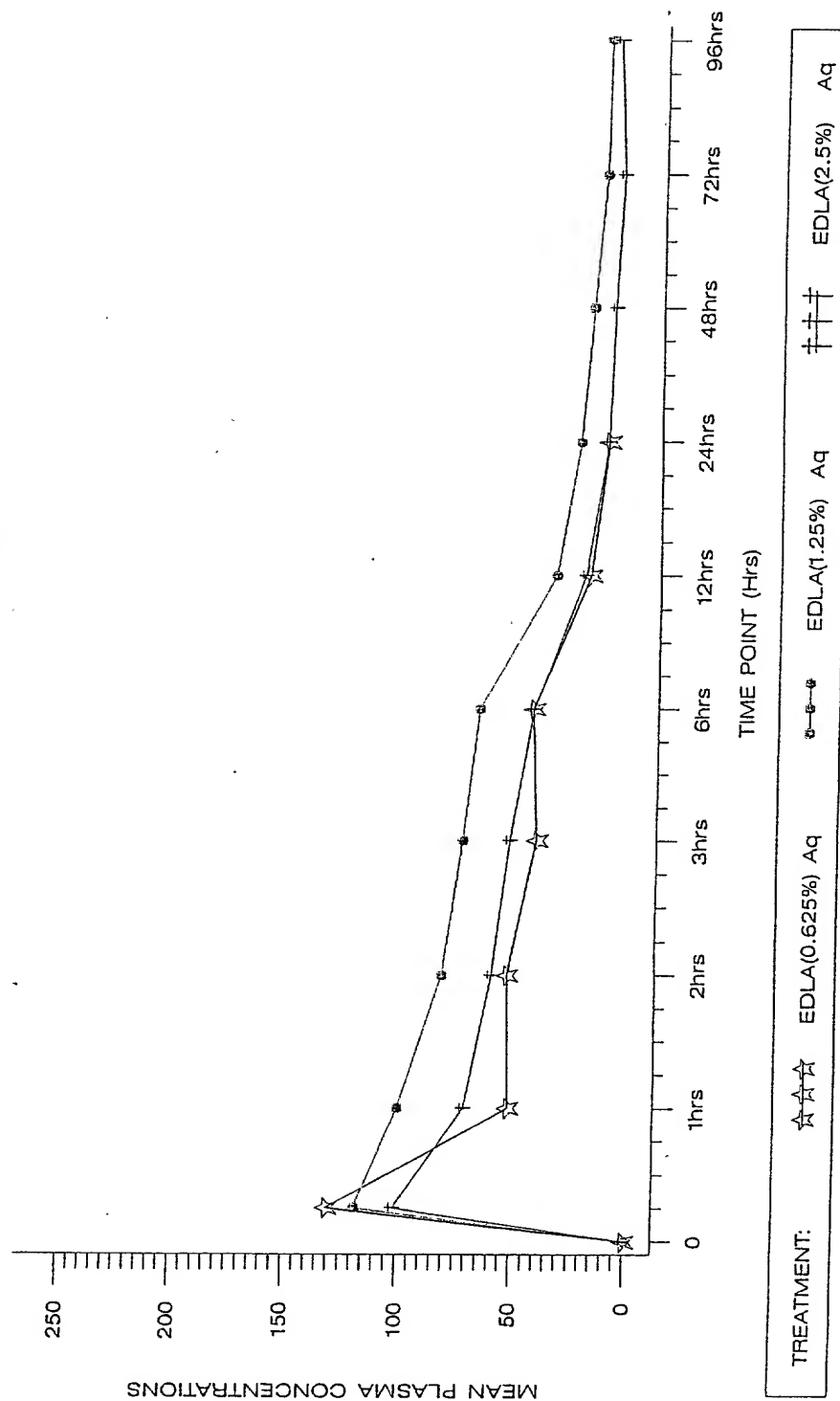
Population: All Subjects Enrolled In Study

STUDY PHASE=3 FORMULA=40K



MEAN PLASMA CONCENTRATIONS OF BUPIVACAINE (ng/ml) BY TIME POINT

Population: All Subjects Enrolled In Study
STUDY PHASE=1 FORMULA=120K



C13

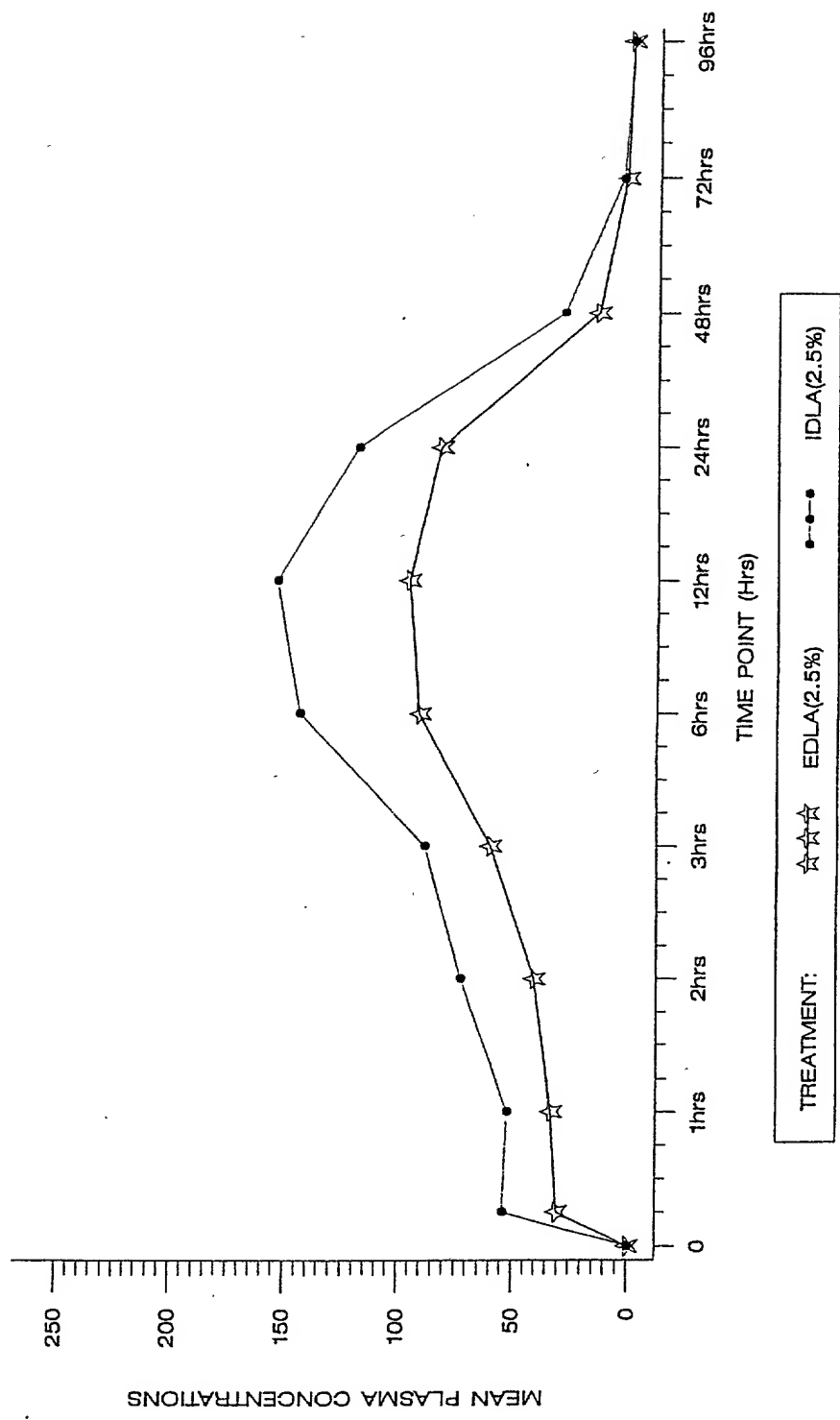
205270 T062500T

FIGURE C13

MEAN PLASMA CONCENTRATIONS OF BUPIVACAINE (ng/ml) BY TIME POINT

Population: All Subjects Enrolled In Study

STUDY PHASE = 2 FORMULA = 40K

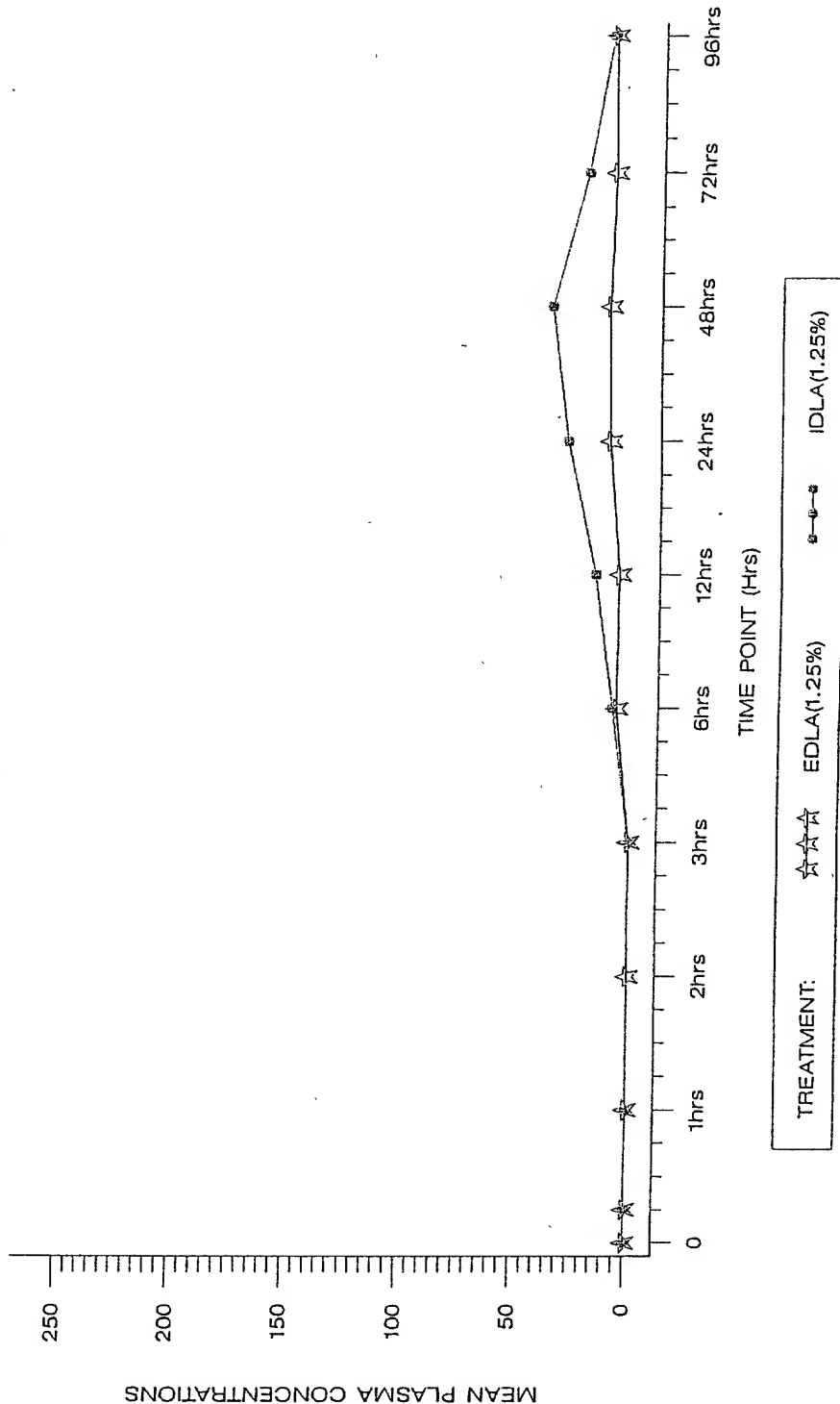


20050719 100025001

FIGURE C14

MEAN PLASMA CONCENTRATIONS OF BUPIVACAINE (ng/ml) BY TIME POINT

Population: All Subjects Enrolled in Study
STUDY PHASE=2 FORMULA=120K

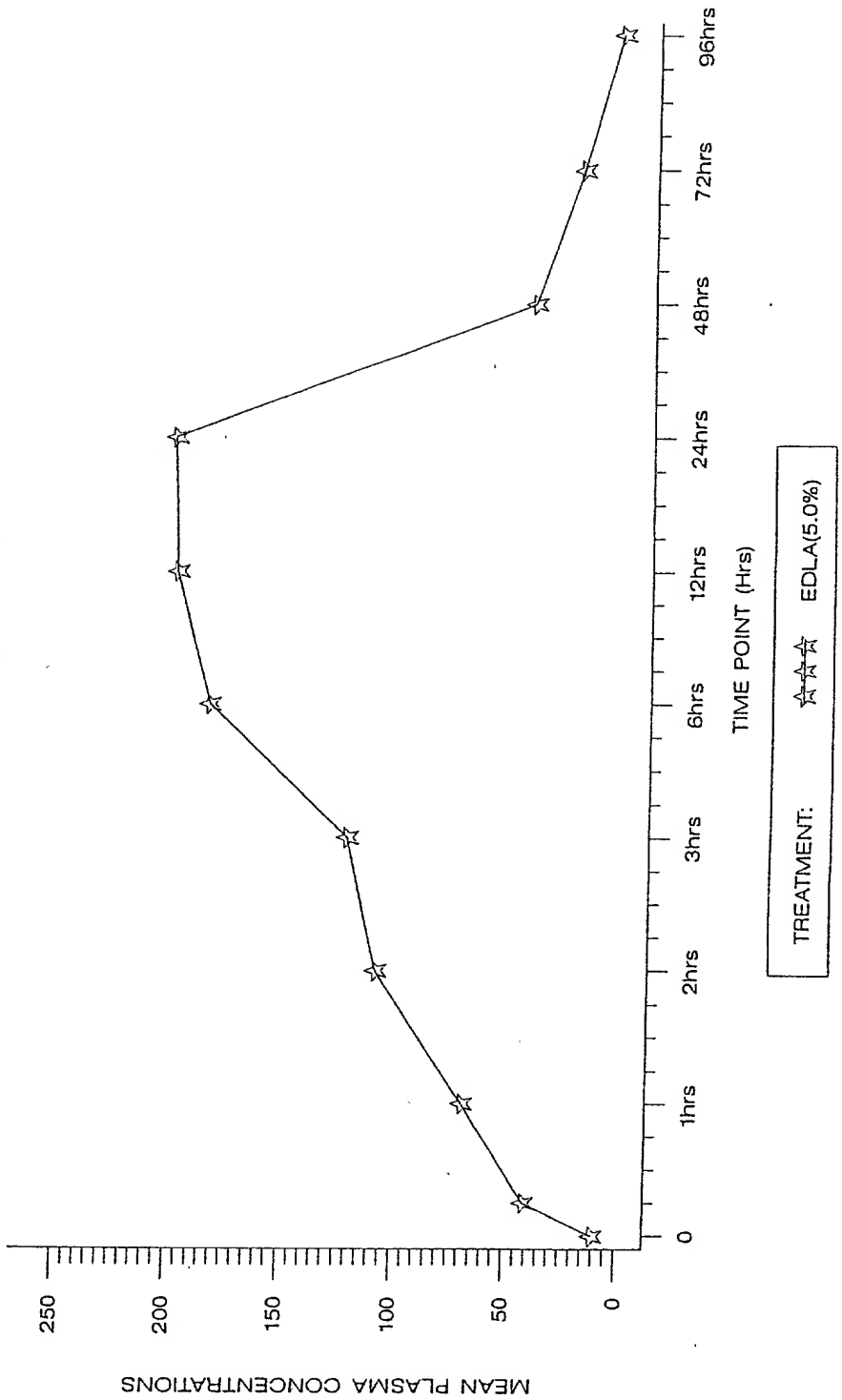


2003-10-10 14:26:00

FIGURE C15

MEAN PLASMA CONCENTRATIONS OF BUPIVACAINE (ng/ml) BY TIME POINT

Population: All Subjects Enrolled in Study
STUDY PHASE=3 FORMULA=40K



10057304 04000

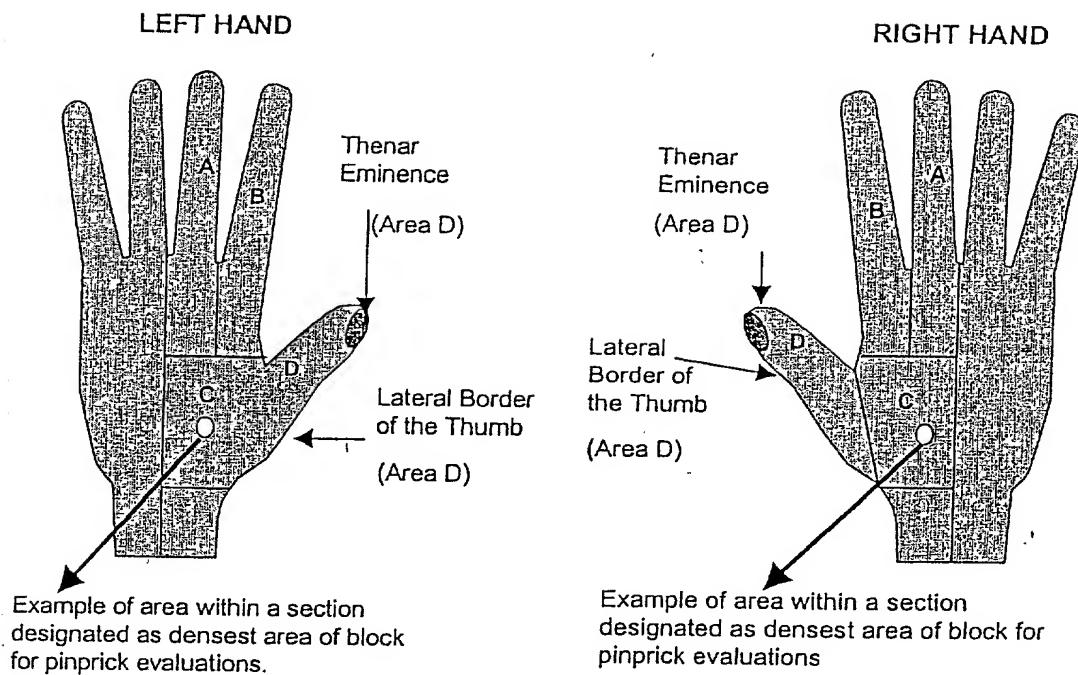
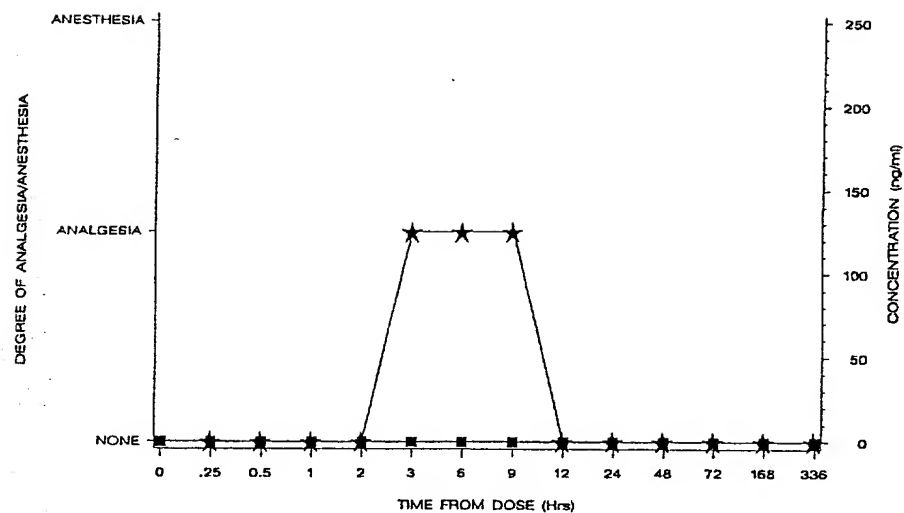
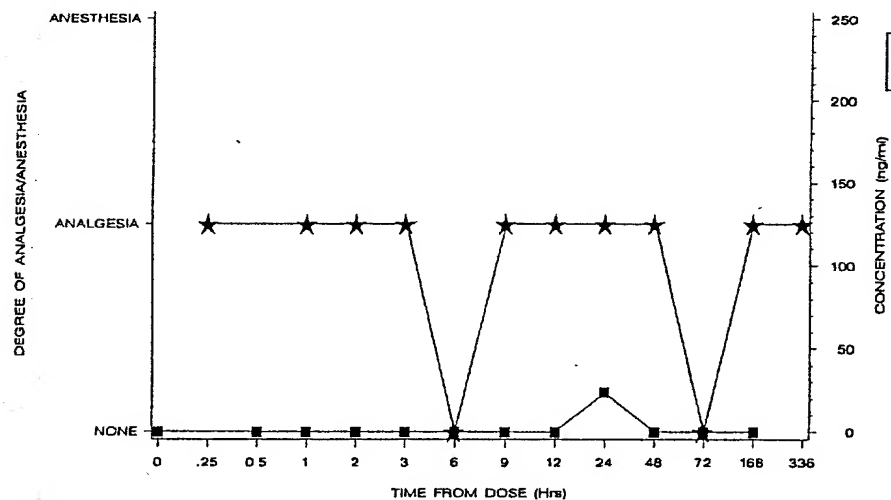


FIGURE D1



13SEP99
Cross References. Appendix 16.2.6.3



13SEP99
Cross References: Appendix 16 2.6.3

FIGURE D2

Degree of Analgesia/Anesthesia in Relation to Plasma Bupivacaine Concentrations for Each Subject Receiving 2.5% 120K EDLA (N = 3)

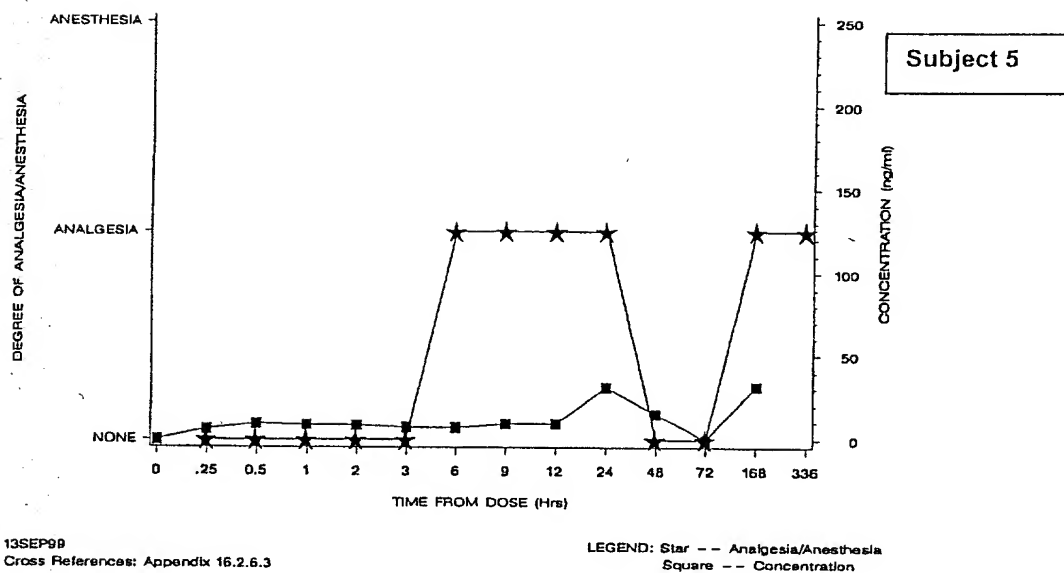
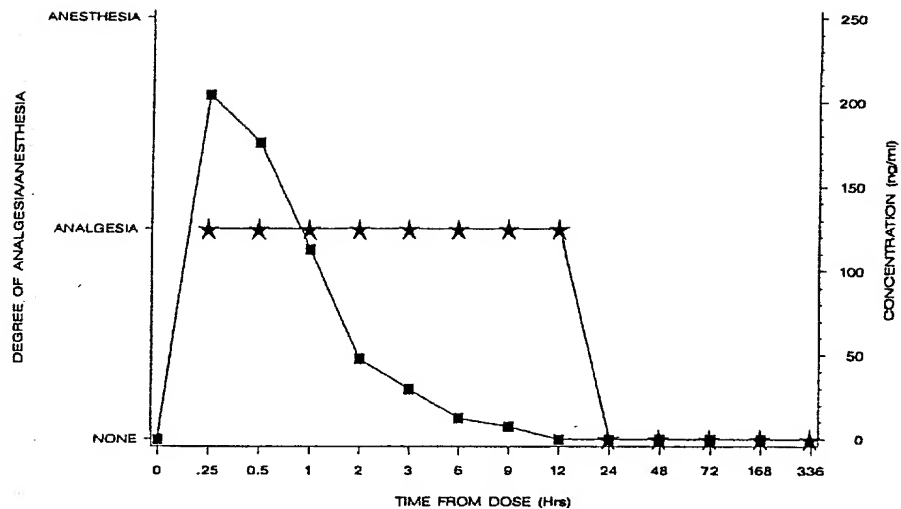


FIGURE D2 (continued)

Degree of Analgesia/Anesthesia in Relation to Plasma Bupivacaine Concentrations for Each Subject Receiving 2.5% 120K EDLA (N = 3)

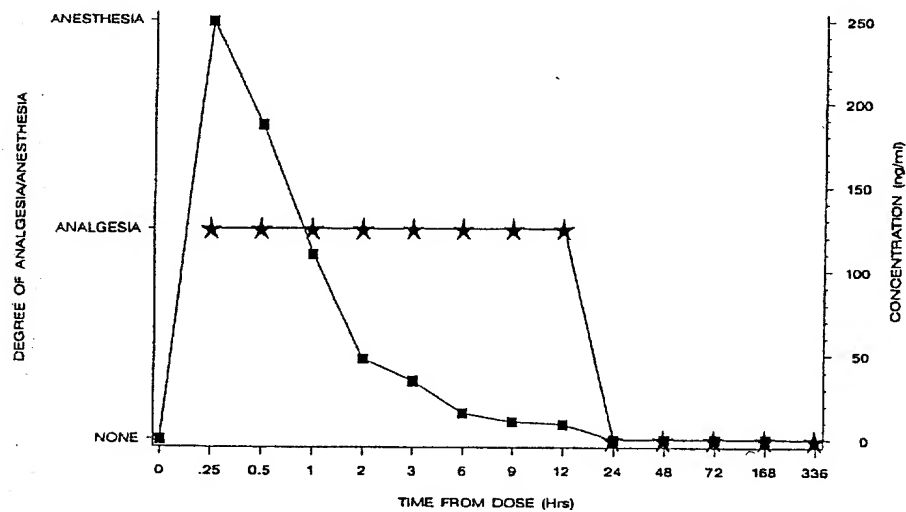
2004-10-10 10:00:00



Subject 2

13SEP99
Cross References: Appendix 16.2.6.3

LEGEND: Star -- Analgesia/Anesthesia
Square -- Concentration



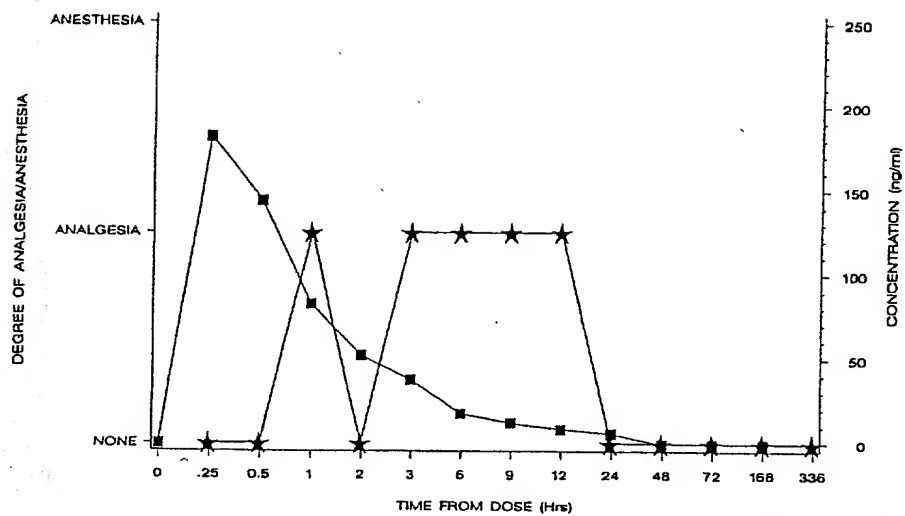
Subject 4

13SEP99
Cross References: Appendix 16.2.6.3

LEGEND: Star -- Analgesia/Anesthesia
Square -- Concentration

FIGURE D3

Degree of Analgesia/Anesthesia in Relation to Plasma Bupivacaine Concentrations for Each Subject Receiving 0.5% AB-D (N = 3)



Subject 6

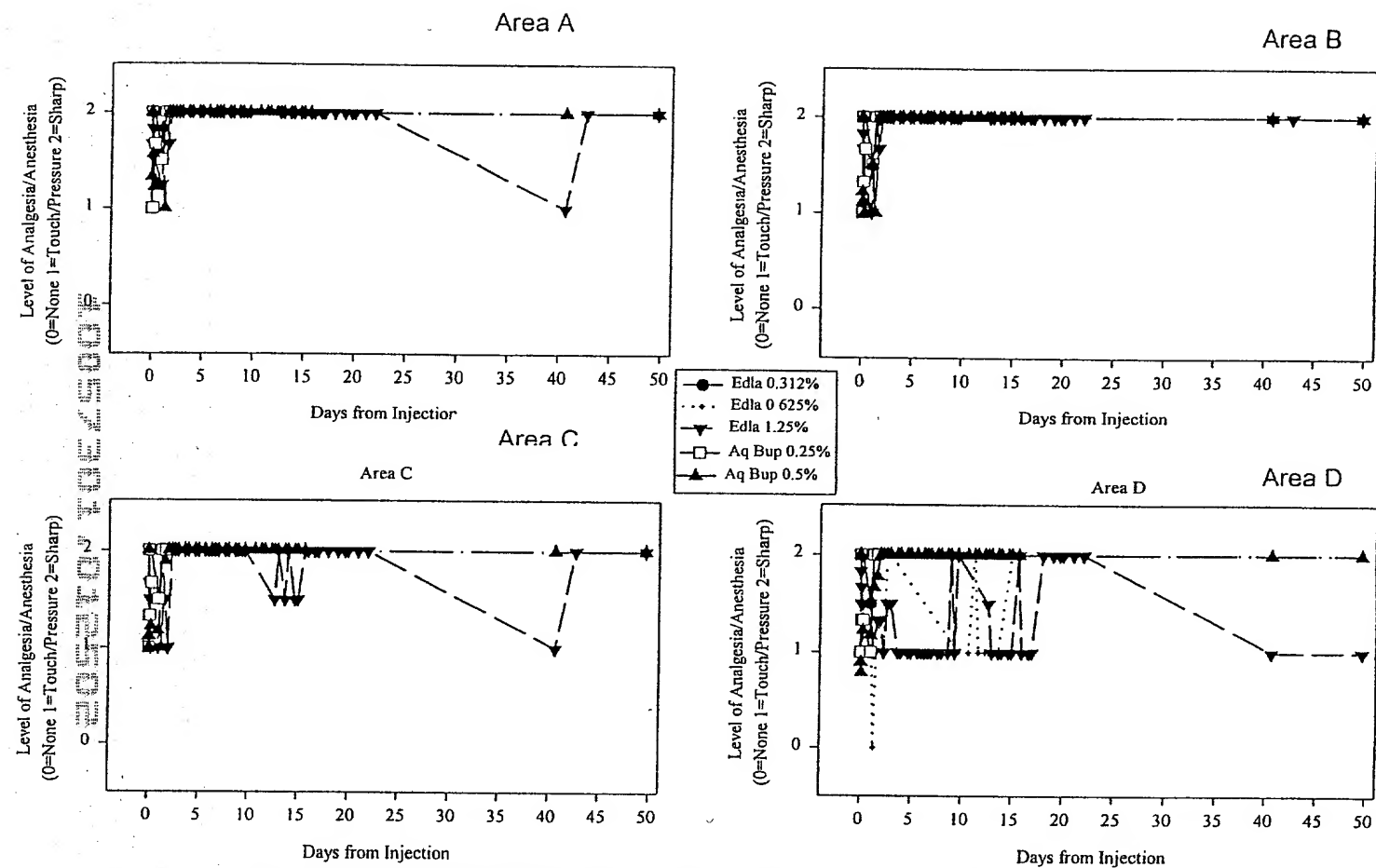
13SEP99

Cross References: Appendix 16.2.6.3

LEGEND: Star -- Analgesia/Anesthesia
Square -- Concentration

FIGURE D3 (continued)

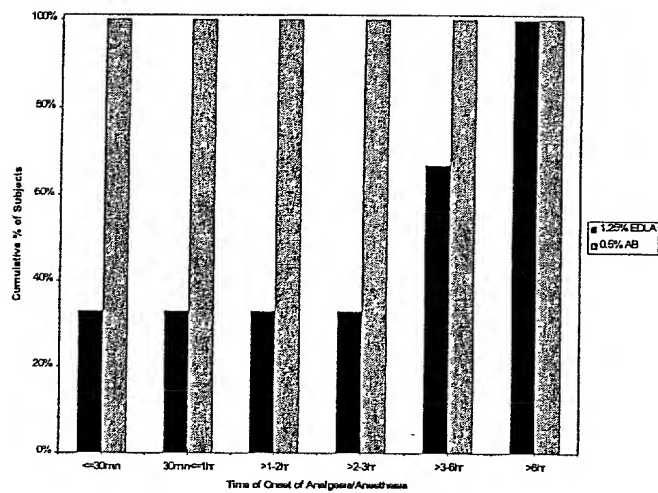
Degree of Analgesia/Anesthesia in Relation to Plasma Bupivacaine Concentrations for Each Subject Receiving 0.5% AB-D (N = 3)



Mean Pinprick Score Over Time, by Each Treatment and for Each Assessment Area

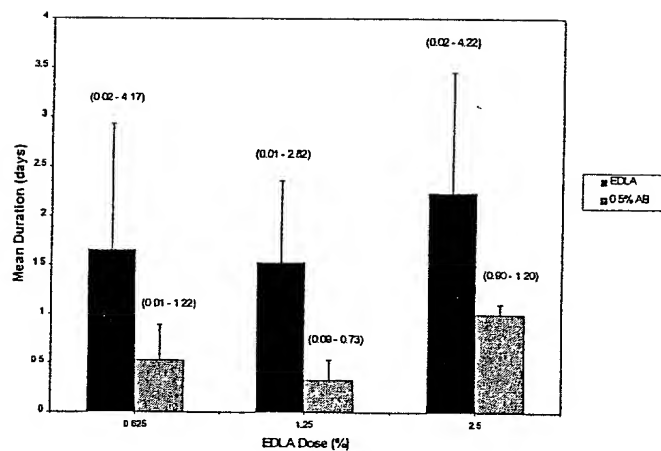
FIGURE E1

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Cumulative Percent of Subjects Demonstrating Onset of Analgesia/Anesthesia Within 6 Hours for 1.25% 40K EDLA versus 0.5% AB.

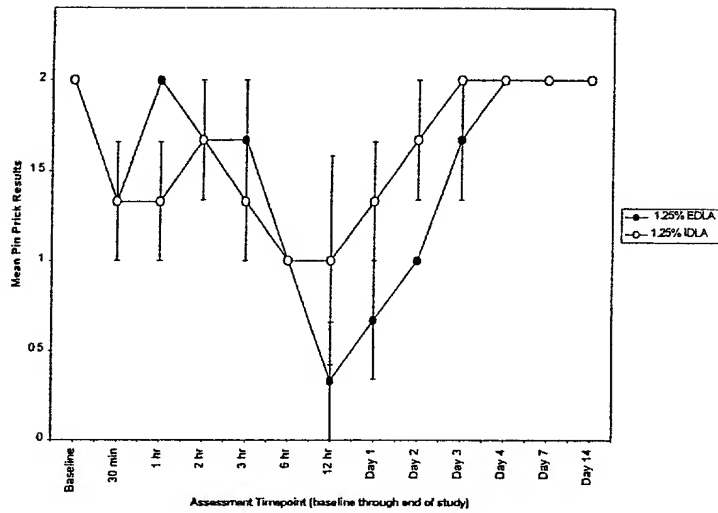
FIGURE F1



Duration of Analgesia/Anesthesia in Area C, by Dose 40K EDLA/AB Study Part I							
		Treatment Pair N=3		Treatment Pair N=3		Treatment Pair N=3	
		40K EDLA 0.625%	AB 0.5%	40K EDLA 1.25%	AB 0.5%	40K EDLA 2.5%	AB 0.5%
Duration	Mean	1.65	0.53	1.53	0.33	2.23	1.00
	(SE)	(1.28)	(0.36)	(0.82)	(0.20)	(1.22)	(0.10)
	Range	0.02-4.17	0.01-1.22	0.01-2.82	0.09-0.73	0.02-4.22	0.90-1.20

Mean (SE) and Range of Duration of Analgesia/Anesthesia by Dose for
40K EDLA versus 0.5% AB

FIGURE F2



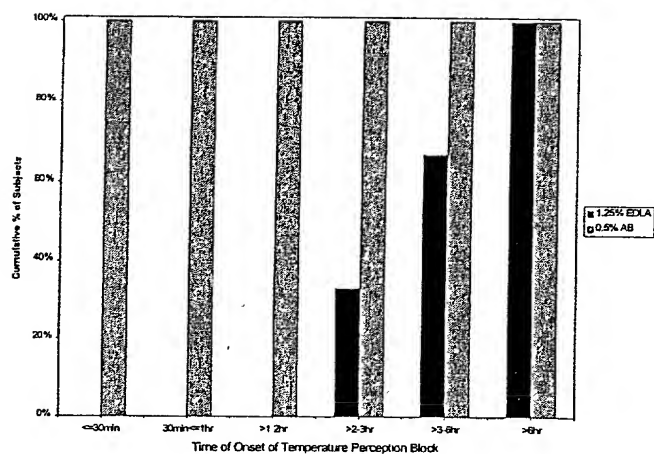
	Base-line	30 min	Hr 1	Hr 2	Hr 3	Hr 6	Hr 12	Day 1 ^b	Day 2 ^b	Day 3 ^b	Day 4 ^b	Day 7 ^b	Day 14 ^b
1.25% 40K EDLA N=3													
Pinprick Test Results ^a													
Mean	2	1.33	2	1.67	1.67	1	0.33	0.67	1	1.67	2	2	2
(SE)	(0)	(0.33)	(0)	(0.33)	(0.33)	(0)	(0.33)	(0.33)	(0)	(0.33)	(0)	(0)	(0)
Range	2-2	1-2	2-2	1-2	1-2	1-1	0-1	0-1	1-1	1-2	2-2	2-2	2-2
1.25% 40K IDLA N=3													
Pinprick Test Results ^a													
Mean	2	1.33	1.33	1.67	1.33	1	1	1.33	1.67	2	2	2	2
(SE)	(0)	(0.33)	(0.33)	(0.33)	(0.33)	(0)	(0.58)	(0.33)	(0.33)	(0)	(0)	(0)	(0)
Range	2-2	1-2	1-2	1-2	1-2	1-1	0-2	1-2	1-2	2-2	2-2	2-2	2-2

^a Evaluated on a scale of 0-2, with 0 = no feeling; 1 = feels touch/pressure; 2 = feels sharp

^b Afternoon investigator results

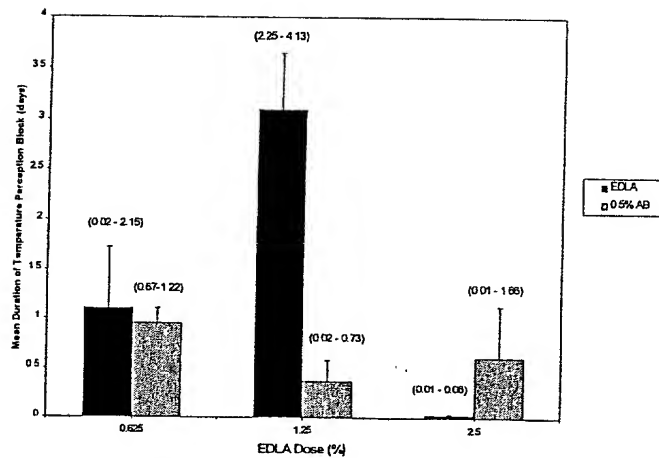
Time Course of Analgesia/Anesthesia in Area C for 1.25% 40K EDLA versus 1.25% 40K IDLA

FIGURE F3



Cumulative Percent of Subjects Demonstrating Temperature Perception Block Within 6 Hours for 1.25% 40K EDLA versus 0.5% AB.

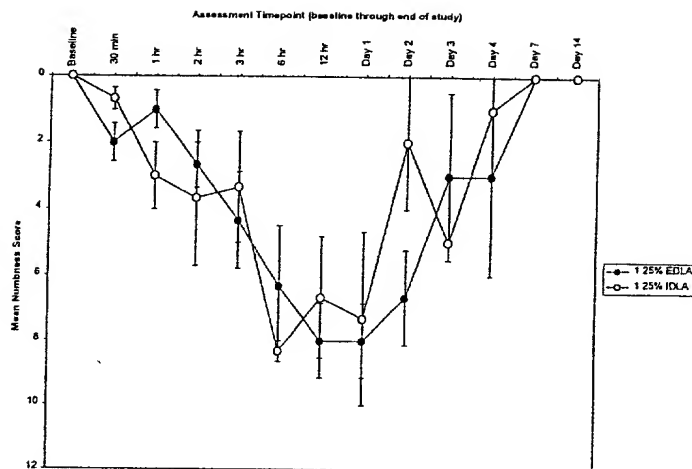
FIGURE F4



Duration of Temperature Perception Block 40K EDLA/AB						
Duration (days)	Treatment Pair		Treatment Pair		Treatment Pair	
	40K EDLA	AB	40K EDLA	AB	40K EDLA	AB
Mean	1.11	0.95	3.10	0.37	0.03	0.61
(SE)	(0.61)	(0.16)	(0.55)	(0.21)	(0.01)	(0.52)
Range	0.02-2.15	0.67-1.22	2.25-4.13	0.02-0.73	0.01-0.06	0.01-1.66

Mean (SE) and Range of Duration (Days) of Temperature Perception Block in Area C for 40K EDLA by Dose.

FIGURE F5



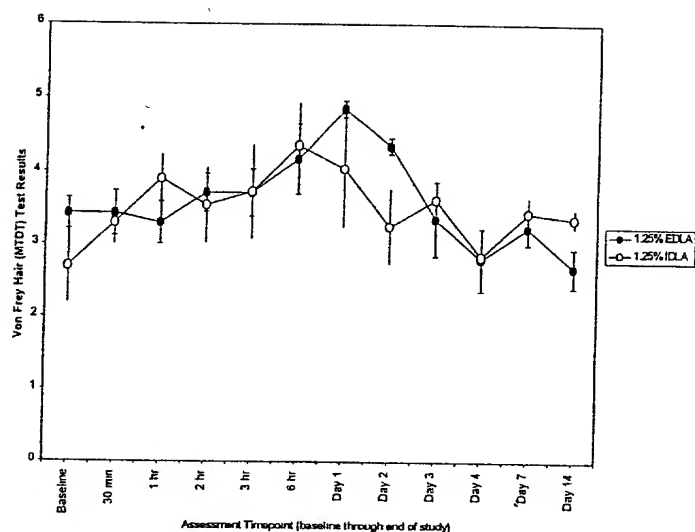
	Base-line	30 min	Hr 1	Hr 2	Hr 3	Hr 6	Hr 12	Day 1 ^b	Day 2 ^b	Day 3 ^b	Day 4 ^b	Day 7 ^b	Day 14 ^b
1.25% 40K EDLA													
N= 3													
Level of Numbness Test Results ^a													
Mean	0	2	1	2.67	4.33	6.33	8	8	6.67	3	3	0	0
(SE)	(0)	(0.58)	(0.58)	(0.67)	(1.45)	(1.86)	(1.15)	(1.15)	(1.45)	(2.52)	(3)	(0)	(0)
Range	0-0	1-3	0-2	2-4	2-7	4-10	6-10	6-10	4-9	0-8	0-6	0-0	0-0
1.25% 40K IDLA													
N= 3													
Level of Numbness Test Results ^a													
Mean	0	0.67	3	3.67	3.33	8.33	6.67	7.33	2	5	1	0	0
(SE)	(0)	(0.33)	(1)	(2.03)	(1.67)	(0.33)	(1.86)	(2.67)	(2)	(0)	(0)	(0)	(0)
Range	0-0	0-1	1-4	0-7	0-5	8-9	3-9	2-10	0-6	5-5	1-1	0-0	0-0

^a Evaluated on a scale of 0-10, with 0 = Not Numb At All, and 10= Totally Numb.

^b Afternoon investigator results

Time Course of Numbness for 1.25% 40K EDLA versus 1.25% 40K IDLA in Area C.

FIGURE F6



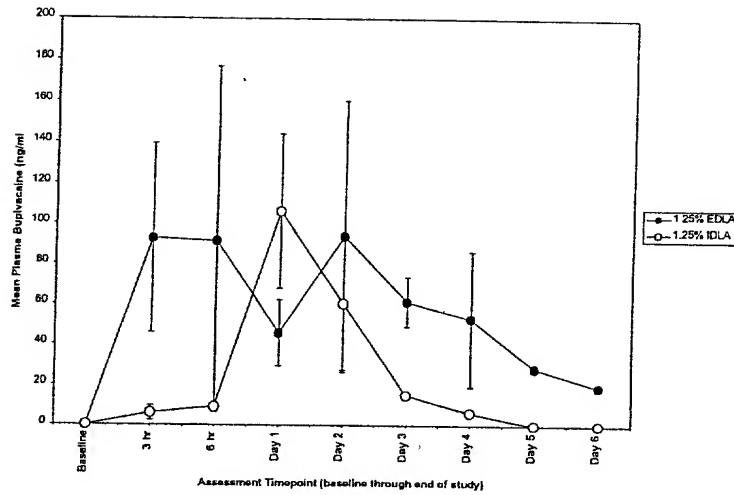
	Base- line	30 min	Hr 1	Hr 2	Hr 3	Hr 6	Day 1 ^b	Day 2 ^b	Day 3 ^b	Day 4 ^b	Day 7 ^b	Day 14 ^b
1.25% 40K EDLA N = 3												
Von Frey Hair (MTDT) Test Results												
Mean	3.43	3.43	3.3	3.71	3.71	4.17	4.85	4.35	3.35	2.79	3.22	2.67
(SE)	(0.21)	(0.31)	(0.29)	(0.26)	(0.32)	(0.48)	(0.11)	(0.11)	(0.51)	(0.43)	(0.23)	(0.27)
Range	3.22- 3.84	2.83- 3.84	2.83- 3.84	3.22- 4.08	3.22- 4.31	3.22- 4.74	4.74- 5.07	4.17- 4.56	2.36- 4.08	2.36- 3.22	2.83- 3.61	2.36- 3.22
1.25% 40K IDLA N = 3												
Von Frey Hair (MTDT) Test Results ^a												
Mean	2.7	3.3	3.9	3.54	3.72	4.36	4.04	3.25	3.61	2.83	3.43	3.35
(SE)	(0.52)	(0.29)	(0.34)	(0.52)	(0.65)	(0.57)	(0.8)	(0.52)	(0)	(0)	(0.21)	(0.13)
Range	1.65- 3.22	2.83- 3.84	3.22- 4.31	2.83- 4.56	2.44- 4.56	3.22- 4.93	2.44- 4.93	2.36- 4.17	3.61- 3.61	2.83- 2.83	3.22- 3.84	3.22- 3.61

^a Evaluated on a scale of 1.65 to 7 with 1.65 being the lowest Von Frey Hair numerical designation and a score of 7 given if the highest Von Frey Hair numerical designation of 6.65 does not produce any sensation of touch.

^b Afternoon investigator results

Time Course of Von Frey Hair Test Results (MTDT) for 1.25% 40K EDLA versus 1.25% 40K IDLA in Area C.

FIGURE F7



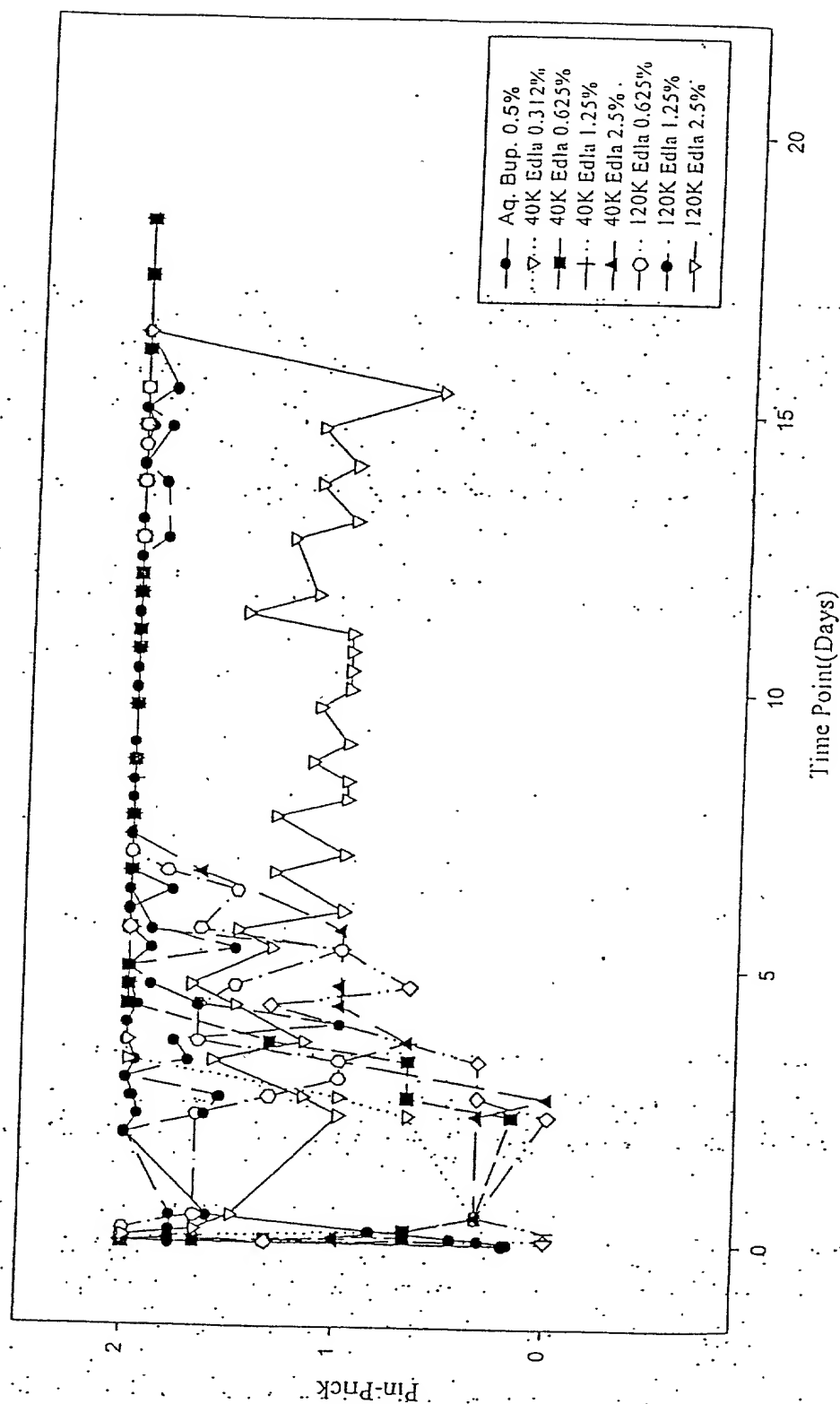
	Baseline	Hr 3	Hr 6	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
1.25% 40K EDLA N = 3									
Plasma Bupivacaine Results									
Mean (ng/ml)	0	92.67	91.55	45.73	93.8	61.27	52.85	28.2	19
(SE)	(0)	(46.77)	(85.23)	(16.51)	(66.43)	(12.33)	(33.45)	(0)	(0)
Range	0-0	0-150	5.48-262	13-65.9	10.1-225	37.1-77.6	19.4-86.3	28.2-28.2	19-19
1.25% 40K IDLA N = 3									
Plasma Bupivacaine Results									
Mean (ng/ml)	0	5.95	8.9	106.03	60.23	14.8	6.28	N.D.	N.D.
(SE)	(0)	(3.56)	(1.95)	(38.18)	(34.06)	(0)	(0)	N.D.	N.D.
Range	0-0	0-12.3	6.01-12.6	30.1-151	20.3-128	14.8-14.8	6.28-6.28	N.D.	N.D.

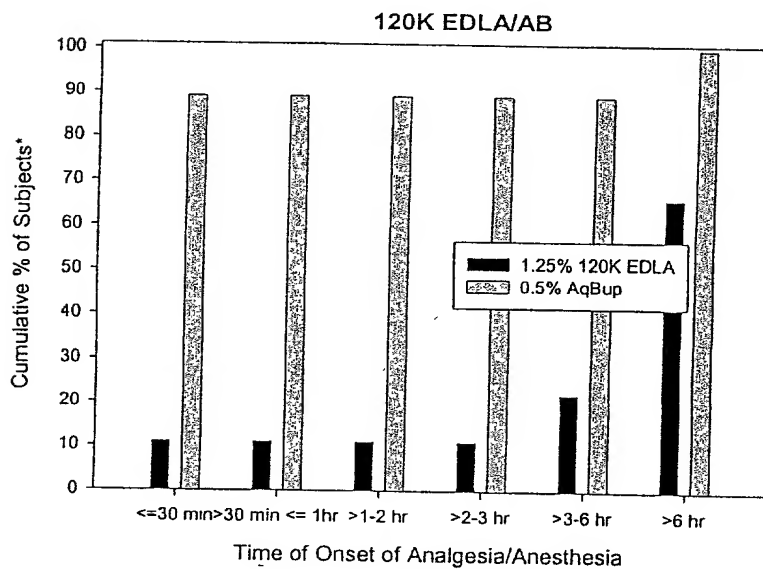
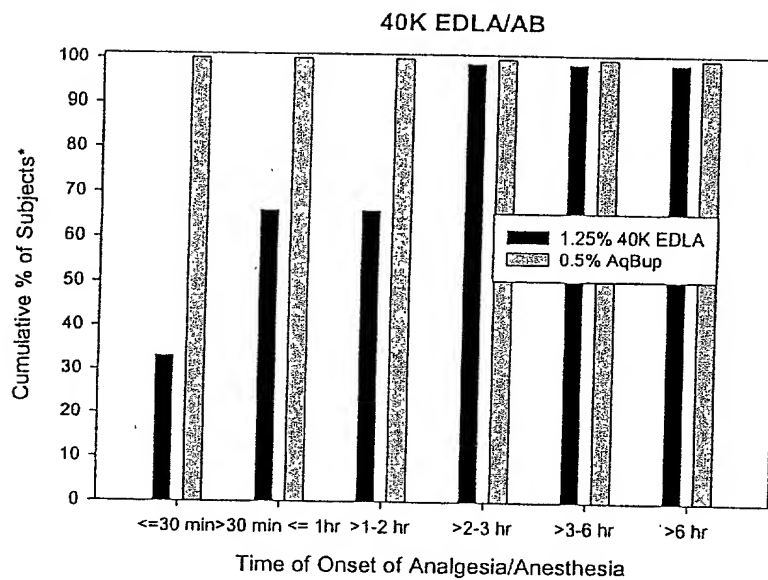
N.D.- Not Detectable

Mean Plasma Bupivacaine Concentrations Over Time (1.25% 40K EDLA and 1.25% 40K IDLA, Volume = 3 mL)

FIGURE F8

Mean Level of Analgesia/Anesthesia Over Time



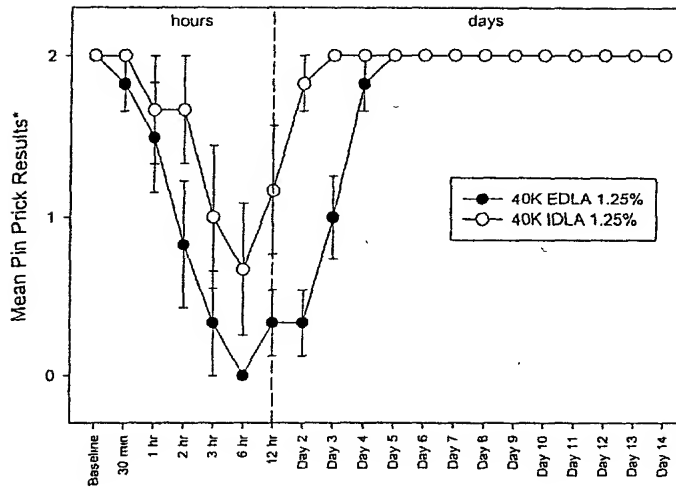


40K EDLA/AB

Cumulative Percent of Subjects Demonstrating Onset of Analgesia/Anesthesia Within 6 Hours for 1.25% 40K and 120K EDLA vs AB.

*Each timepoint represents an accumulation until the highest group value achieved.

FIGURE G2



Assessment Timepoint (baseline through end of study)

	Base -line	30 min	h 1	h 2	h 3	h 6	h 12	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
40K EDLA 1.25%													
	N=6 ^a												
Pinprick Score ^b													
Mean	2	1.8	1.5	0.8	0.4	0	0.3	0	1.0	1.8	2.0	2.0	2.0
(SE)	(0)	(0.2)	(0.3)	(0.4)	(0.3)	(0)	(0.2)	(0)	(0.3)	(0.2)	(0)	(0)	(0)
Range	2, 2	1, 2	0, 2	0, 2	0, 2	0, 0	0, 1	0, 1	0, 2	1, 2	2, 2	2, 2	2, 2
40K IDLA 1.25%													
	N=6												
Pinprick Score ^b													
Mean	2	2	1.7	1.7	1.0	0.7	1.2	2.0	2.0	2.0	2.0	2.0	2.0
(SE)	(0)	(0)	(0.3)	(0.3)	(0.5)	(0.4)	(0.4)	(0)	(0)	(0)	(0)	(0)	(0)
Range	2, 2	2, 2	0, 2	0, 2	0, 2	0, 2	0, 2	1, 2	2, 2	2, 2	2, 2	2, 2	2, 2

^a EDLA and IDLA blocks were administered bilaterally to 6 subjects who received one treatment in one foot and the other treatment in the opposite foot.

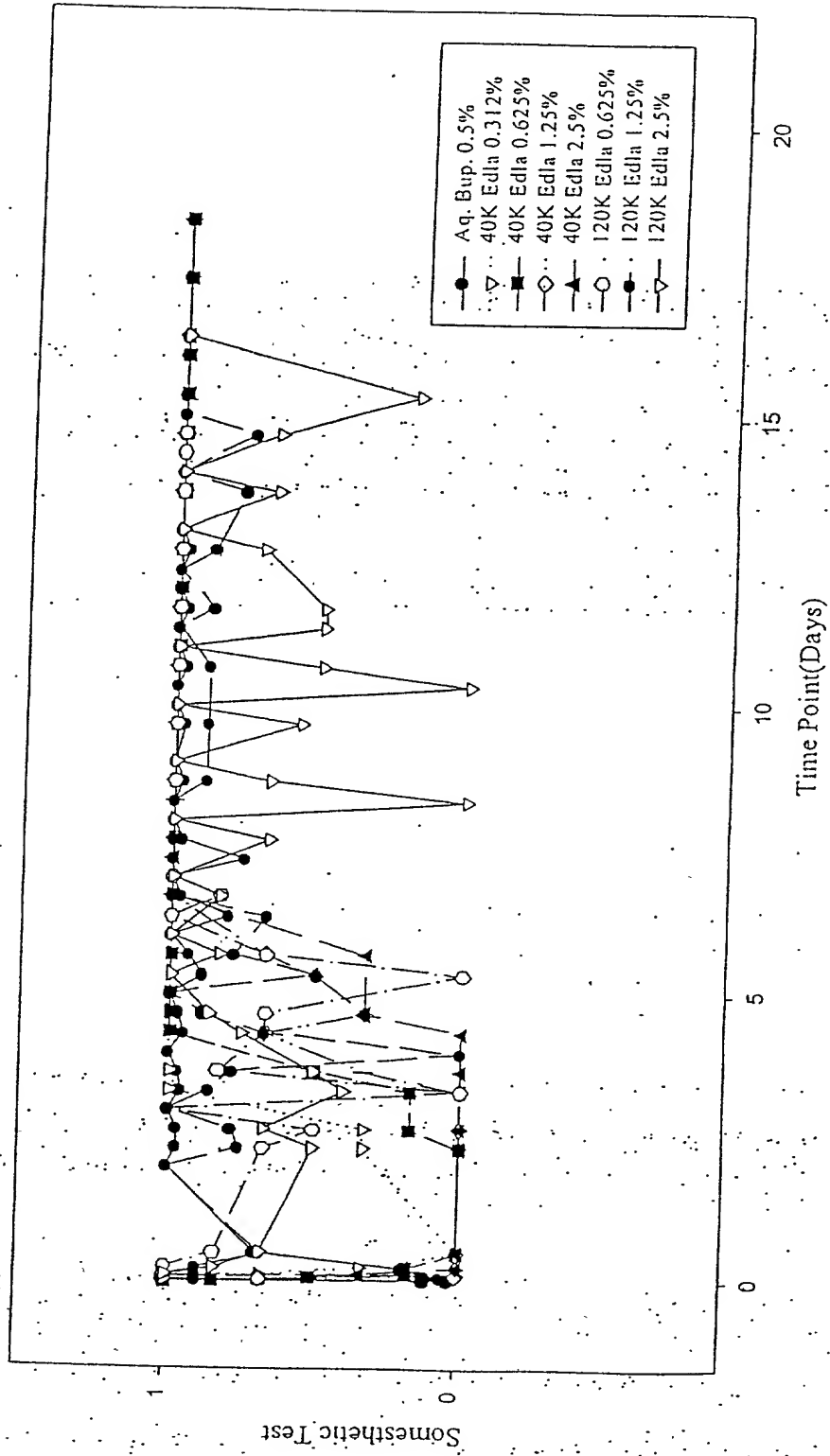
^b Evaluated on a scale of 0-2, with 0 = no feeling; 1 = feels touch/pressure; 2 = feels sharp.

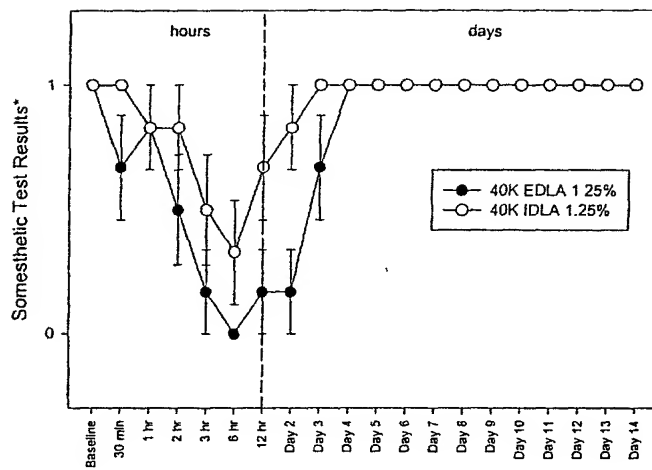
Mean (SE) and Range of Pinprick Scores Over Time
for 1.25% 40K EDLA vs 1.25% 40K IDLA

FIGURE G3

FIGURE G4

Mean Level of Temperature Perception Blockade Over Time for Treatments Combined - Top of Foot
Part I





Assessment Timepoint (baseline through end of study)

	Base -line	30 min	h1	h2	h3	h6	h12	Day 2 ^b	Day 3 ^b	Day 4 ^b	Day 5 ^b	Day 6 ^b	Day 7 ^b
40K EDLA 1.25%													
N=6													
Temperature Perception Score ^a													
Mean	1	0.7	0.8	0.5	0.2	0	0.2	0.2	0.7	1.0	1.0	1.0	1.0
(SE)	(0)	(0.2)	(0.2)	(0.2)	(0.2)	(0)	(0.2)	(0.2)	(0.2)	(0)	(0)	(0)	(0)
Range	1, 1	0, 1	0, 1	0, 1	0, 1	0, 0	0, 1	0, 1	0, 1	1, 1	1, 1	1, 1	1, 1
40K IDLA 1.25%													
N=6													
Temperature Perception Score ^a													
Mean	1	1	0.8	0.8	0.5	0.3	0.7	0.8	1.0	1.0	1.0	1.0	1.0
(SE)	(0)	(0)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0.2)	(0)	(0)	(0)	(0)	(0)
Range	1, 1	1, 1	0, 1	0, 1	0, 1	0, 1	0, 1	0, 1	1, 1	1, 1	1, 1	1, 1	1, 1

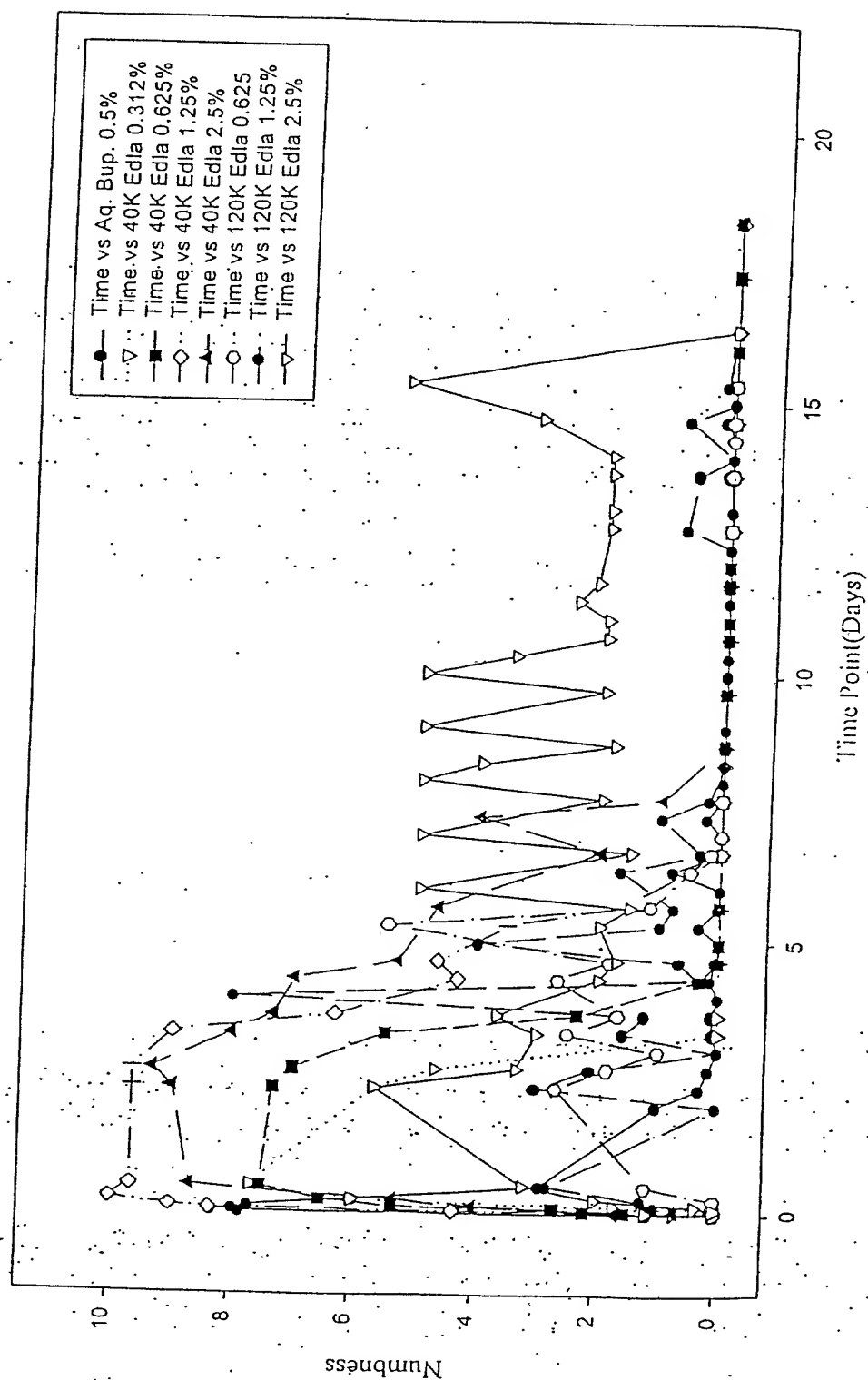
^a Evaluated on a scale of 0-1, with 1 = "yes" (a change in temperature was perceived), and 0 = "No" (no change in temperature was perceived). ^b Evening score.

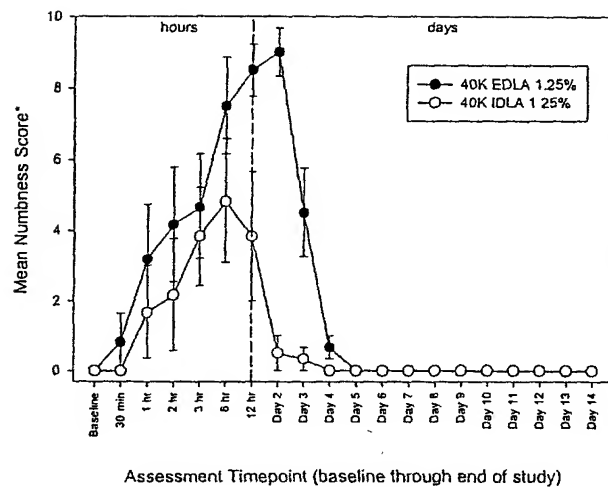
Mean (SE) Scores of Temperature Perception for 1.25% 40K EDLA vs
1.25% 40K IDLA

FIGURE G5

FIGURE G6

Mean Level of Numbness Over Time for Treatments Combined - Top of Foot
Part I





	Base -line	30 min	h1	h2	h3	h6	h12	Day 2 ^b	Day 3 ^b	Day 4 ^b	Day 5 ^b	Day 6 ^b	Day 7 ^b
40K EDLA 1.25%													
N=6													
Level of Numbness Score ^a													
Mean	0	0.8	3.2	4.2	4.7	7.5	8.5	9.0	4.5	0.7	0	0	0
(SE)	(0)	(0.8)	(1.6)	(1.6)	(1.5)	(1.4)	(0.7)	(0.7)	(1.3)	(0.3)	(0)	(0)	(0)
Range	0	0, 0.5	0, 10	0, 10	1, 10	2, 10	6, 10	6, 10	0, 8	0, 2	0	0	0
40K IDLA 1.25%													
N=6													
Level of Numbness Score ^a													
Mean	0	0	1.7	2.2	3.8	4.8	3.8	0.5	0.3	0	0	0	0
(SE)	(0)	(0)	(1.3)	(1.6)	(1.4)	(1.8)	(1.8)	(0.5)	(0.3)	(0)	(0)	(0)	(0)
Range	0	0	0, 8	0, 10	0, 10	0, 10	0, 10	0, 3	0, 2	0	0	0	0

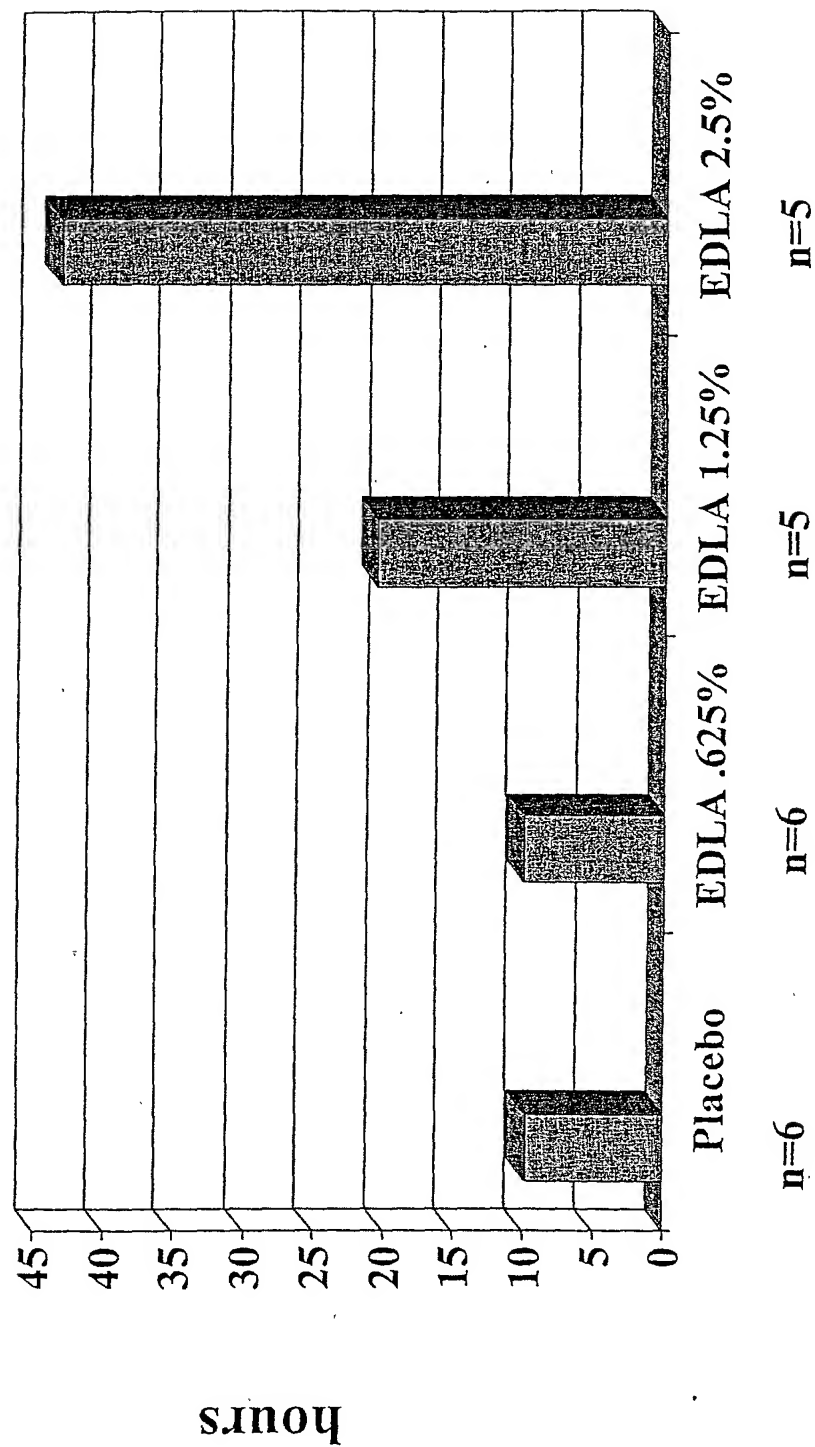
^a Evaluated on a scale of 0-10, with 0 = Not Numb At All, and 10= Totally Numb.

Mean (SE) Numbness Scores for 1.25% 40K EDLA vs 1.25% 40K IDLA.

FIGURE G7

Figure H1

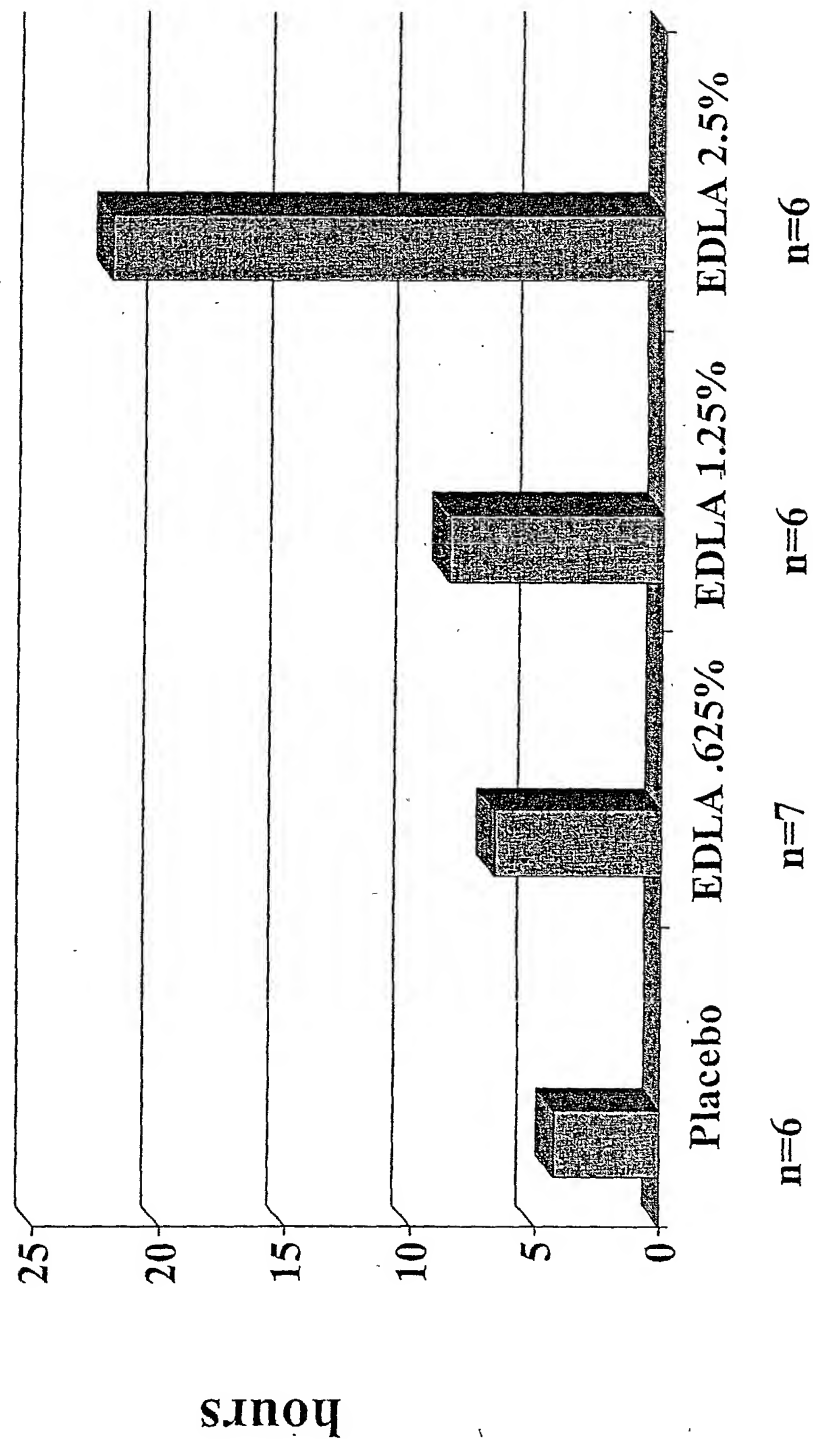
Median Time to First Pain > 3
(ITT)



Log rank test, $p=0.0498$

Figure H2

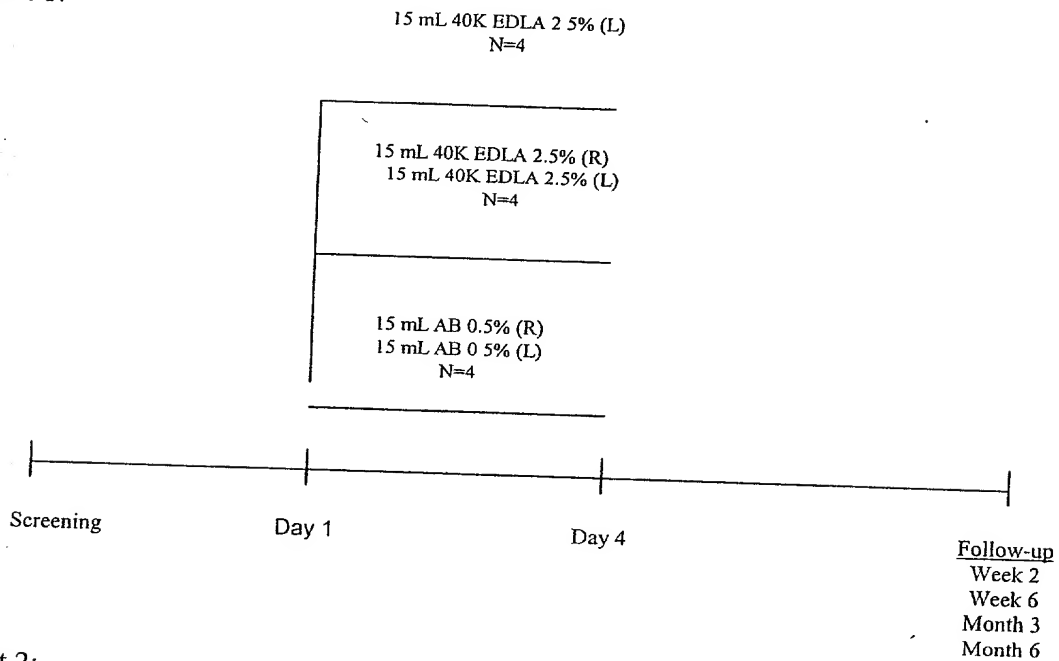
Median Time to First Rescue (ITT)



Log rank test, $p=0.0032$

FIGURE J-1
Microdialysis Study Design

Part 1:



Part 2:

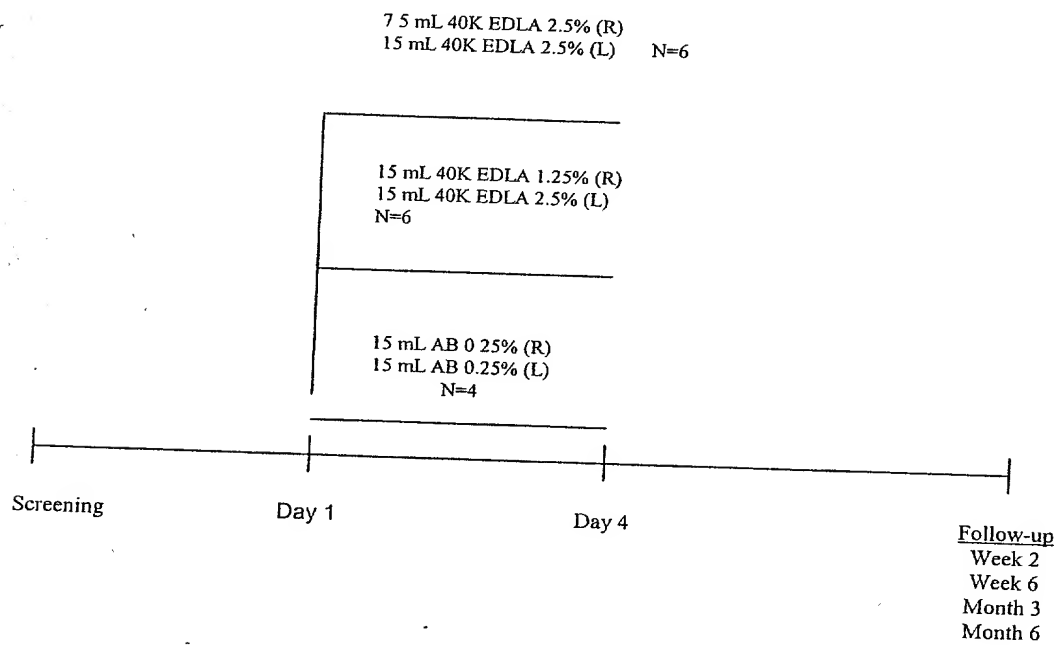


FIGURE J-2

Injection and Probe Placement

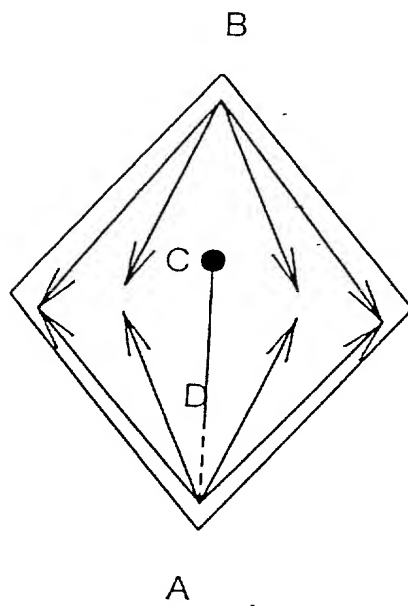


FIGURE J-3

Subject Disposition

